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SYNTHESIS OF SUPRAMOLECULAR COMPLEX L– (-) – MENTHOL

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ABSTRACT

In this article glycyrrhizic acid content with menthol in several various proportions (2:1; 4:1; 9:1), information was given on synthesis and physical and chemical properties of new supermolecular complexes. Received supramolecular complexes concerning 4:1 it was chemically defined and also studied structure of supramolecular complexes by physical methods on the basis of interaction of organic molecules with electromagnetic radiation, in particular their range IR – of spectroscopy. Our work of the near future will be turned to check it recently supramolecular complexes on the basis of GA: Menthol for growth of a plant and biotic elasticity of tension.

Key words: *glycyrrhizic acid, menthol, receptor, substrate, supramolecular complex, IR spectrum, chromatography, functional groups, organic solvent, «guest-host» system.*

Introduction

Glycyrhizic acid (GA) [40], [41] (20 β-carboxy-11-oxo-30-norolean-12-en-3 β-il-2-O-β-D-glucopyranuronosyl-α-D-glucopyranose-duronic acid) is a valuable raw material, which is important in the food industry, cosmetology, and other industries. Based on the chemical structure of glycyrrhizic acid, it is a glycoside, which is formed by glucuronic acid residue with triterpene-glycyrrhizic acid [1], [2]. (Figure 1A).

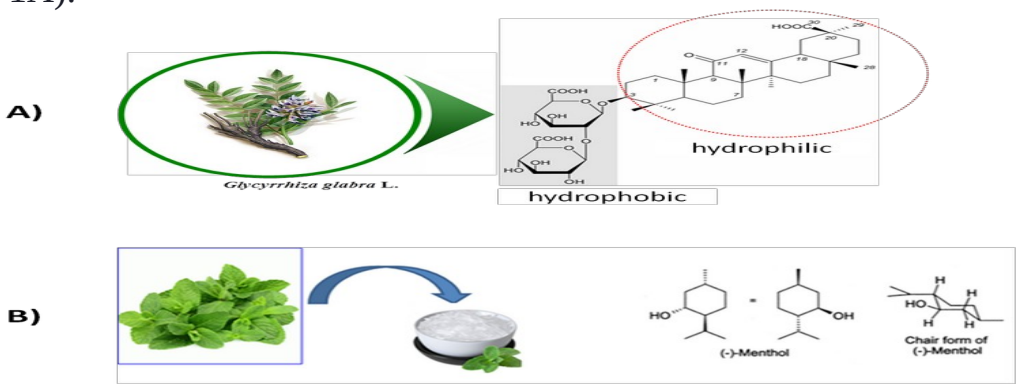

Figure 1A. Molecular structures of Glycyrrhizic acid (Empirical formula - $C_{42}H_{62}O_{16}$; 20β -carboxy-11-oxo-30-norolean-12-en-3 β-il-2-O- β -D-glucopyranuronosyl- α-D-glucopyranose-duronic acid) [2].

Many studies on the physical-chemical features of GA showed the molecule contains hydrophobic (triterpene fragment) and hydrophilic (two glucuronide residues) parts that are assumed to make a mycelium in the complexes [3].

The GA is extracted from the root of licorice (*Glycyrrhiza glabra L.* and *Glycyrrhiza uralica L.*) [4]. Several compounds of GA were obtained and used for various purposes. The GA can be easily formed with other molecules to make a supramolecular compound called a «*guest-hos*» type [5]. Other studies were also confirmed that GA provides a «host-guest» type of auto association [6], [7], [8].

The supramolecular complex of GA is characterized as a ring dimer structure with hydrophobic cavities due to intermolecular hydrogen bonds. This cavity can provide a «*guest-host*» type formation [9].

The GA reacts with many other molecules to yield a supramolecular complex [10], [11], [12], [13], [14]. Particularly, increasing GA concentration stimulated the auto association of the «guest-host» type of supramolecular complex with streptomycin under the various ratio of GA: streptomycin (1:1, 2:1, 3:1, 3:2) [15].

At present, a lot of supramolecular complexes based GA with various agents were chemically synthesized and used in various fields. For instance, before sowing wheat seed treated GA and its denatured salt combined with «Tebukonazol» enhanced the resistance to various pathogenic infections at the early stage of plant organogenesis and increased yield productivity [8]. It is assumed that GA molecules (~60–100) form vesicles/mycelium and provide increased transmembrane penetration with the main drug molecules involved [8].

The therapeutic dosage of some medicines can often cause adverse effects [16], [17]. It is worth noting that positive results are obtained based on the use of supramolecular compounds of GA. For example, a supramolecular complex of GA and streptomycin can reduce the dose of the drug used [18], [19]. Supramolecular complexes are used in practice as an effective method of increasing the water solubility level of pharmacological preparations based on mechanical and chemical mechanisms. In particular, studies have shown a significant increase in the solubility levels of drugs such as Diazepam (Sibazon), «Nifedipine», «Ibuprofen». It is assumed that this is due to the physicochemical properties of the micelles that form the GA molecule [8].

Menthol ($C_{10}H_{20}O$) is a terpenoid that found in the essential oils of the mint family (Mentha sp.). It is a white crystalline solid that can dissolve well at room temperature or partially at high temperatures. There are several isomers of menthol including iso-menthol, neomenthol, neo-isomenthol with peppermint odor. Among them, (-) menthol (1R, 2S, 5R)-2-isopropyl-5-methylcyclohexaneanol) is one of the strong aromatic molecules in nature (Figure 1B).

Figure 1B. Molecular structures of menthol ($C_{10}H_{20}O$);

The (-) Menthol is a known with strong cooling and refreshing agent and four times higher efficacy than (+) menthol isomers [20]. Therefore, some of its derivatives are widely used in medicine, pharmaceutics, perfumery and food industries. Menthol cools the skin when it applied to the skin; therefore it is used as a medicine during the headache. Moreover, (-) menthol can also use as antiseptic properties to nose and throat mucus [21]. Nowadays, one of the crucial tasks in agriculture involves the enhancing of plant productivity with sustainable chemicals. In the present research, the GA was extracted from the licorice root and synthesized it's a supramolecular complex with menthol.

Materials and methods

The spectrophotometric methods for quantitative/qualitative chemical identification of GA in biomaterial content are used effectively [22-25]. Some researchers have noted the efficacy of *Glycyrrhiza glabra L.* root mass extraction in high-temperature aqueous environments, in the next step, the formation of low concentrations in a vacuum apparatus, HNO_3 solution (3%) and extraction of GA based on acetone extracting [26]. Another study used an NH_4OH (1%) for the extraction of GA from the root of the licorice. In case, the acid was removed by H_2SO_4 solution [27].

Extraction of GA. Some methods are available to extraction and chemical identification for the GA from licorice (*Glycyrrhiza glabra L.)* root [28]. We have used a local licorice root from a Sirdarya region, Uzbekistan. Approximately 100mg which is 92% technical GA dissolved with 3% Sulphate acid and boiled in a water bath until to get a white powder. After then this product was cooled at room temperature overnight. The contents then were filtered with filter paper and washed with cold distilled water. Final extract dried and stored in a dark condition for further experiment. Purity: 92%, T_{liq} = 210-213 ^{0}C / a / D25 = +48 (dis. water. Ethanol 1: 1); R_f =0.83 (1), Yield: 98%. IR spectra: 1041 cm-1 (-O-); 1656 cm^{-1} (CO); 2873 cm^{-1} (CH_3); 3247 cm^{-1} (OH).

Identification of GA. Chemical identification of GA was performed by using standard methods which are mentioned in some reference [29-30]. In our experiments, root extract was analyzed by using a Perkin Elmer Spectrum IR (Germany; version 10.6.1) IR-Fure spectrometer in the range of 4000–500cm^{-1}. KBr tablet was used as a standard GA for the preparation of test samples. The IR spectra of GA and β-indolyl-3-acetic acid were compared with the spectra of the «Biochemica» Biblioteca.

Obtaining a supramolecular complex.

Supramolecular compounds were obtained by the following steps. Firstly, 1.68g (0.002M) of GAMAT dissolved 25ml distilled water and 25ml ethanol. This solution widely mixed with a magnetic stirrer at 50-60^{0}C. Then we added 0.156g (0.001 M) Menthol and continued the mixing process for 5-6 hours. After then the reaction mixture was filtered. The rest of the ethanol was removed in a vacuum, and the aqueous part was dried in a lyophilic manner. Final product was a yellow powder: liquid=205-210^{0}C Rf=0.9 (System 2) Units: 85% IR spectrum: 1042 (-O-)

cm^{-1}; 1655 (CO) cm^{-1} 2948 (CH_3) cm^{-1}; 3600-3200 (OH) cm^{-1}. Other supramolecular complexes of GA with Mt were also obtained by this synthesis method:

1. GA:MT (2: 1). Liquid = 218-220 ^{0}S R_f= 0.8 (System 2) Productivity 95%
2. GA:MT (4: 1). Liquid = 220-225^{0}S, R_f (1) Productivity: 90%.

Reagents and equipment

In our experiment, we have used ethanol, benzene, acetone acid solutions, as well as alkaline solutions as organic solvents for dissolving. The Chromatography (TLC) was used for thick layer:

1) benzene: acetone 5:3;
2) acetonitrile: water 1:2;
3) benzene -efir 15:3;
4) benzene: acetone 5:1;
5) acetone: Alcohol is treated with 1:1.

10% alcohol solution of sulfuric acid (H_2SO_4) and iodine chamber for chromatography staining were monitored.

Continuously stirring was performed by using a magnetic mixer MM-5 TU 25-11834-80. The organic solvent was evaporated from the system on an IR-1M2 rotor evaporator. For drying we have used the Automatic FREEZE-Dryer10-010, a lyophilic device and PTP TU 25-11-1144 unit were used to measure the fluid temperature of the substances. The structure of supramolecular complexes was performed on the IR spectrometer FT-IR System-2000. The Silufol (Czech Republic) plates were used for thin-layer chromatography.

Preparation of a working standard solution for glycyrrhizic acid:

0.10 precise drawer was weighed on analytical weight and placed in a 100ml measuring tube. 10ml 96% ethanol was added, diluted thoroughly and filled with distilled water to the measuring line (Solution A). After thoroughly shaking the tube, 1 ml of aliquots were taken and diluted with 9 ml. fluid system (Solution B, working standard solution), 0.1mg/ml. The standard working solution was placed on a chromatograph for analysis.

Preparation of the solvent system:

14 ml of acetonitrile and 0.5ml of acetic acid and water-filled till 50ml tube. This solution (pH 3.0-3-5) always used in our work.

Results and discussion

Currently, modern physic-chemical methods are available for GA extraction including boiling of root tissue at high-temperature water [26, 31], NaOH aqueous solution [32], methanol [33], ethanol [34-35], and the use of ammonia solutions. As well as, the vacuum-pulse methods [32], ultrasound [36] also used to increase the efficiency of extraction.

In our experiment, local licorice (Glycyrrhiza glabra L.) roots were washed with distilled water and dried. Then the roots were mechanically milled to <0.5–1 mm size. Extra agents were selected according to the literature data [37]. Firstly, pieces of the roots were cracked in 70% ethanol at 1:5 ratios and kept in dark for 5

days that stirring constantly. In the next step, the extract was filtered and the ethanol was evaporated under + 75 ° C [38]. The mass column (h = 20 cm; ø = 2.5 cm) was divided into fractions (3) by using a chromatography. The elution was carried out in 1% ethanol (75%) of the ammonia solution. The fractions were analyzed by using high-performance liquid chromatography 1200 series DAD detector with Agilent Technologies (USA), high-performance liquid chromatography (150×4.6 mm); 5 µm) at +20°C. The flow rate value of the moving phase shows a 0.5 ml/min. The methanol and an acidic acid solution (0.05%) were used as the active phase. Detection was carried out in the 250 nm, 275 nm, and 350 nm full-length sectors. As a standard sample, we have used ammonium salts of GA (Sigma-Aldrich, Germany). In results, the higher concentration of the GA can observe at a second fraction (Table 1).

Table 1. Quantification of GA from root tissue extract of the licorice (Glycyrrhiza glabra L.).

Fractions	**Concentration** (in accordance with dry specimen, mg/g)	**Weight share** (%)
1	2,4	0,24
2	5,8	0,65
3	3,6	0,38

Our next experiment was root biomass (5±0.5 g) of licorice (*Glycyrrhiza glabra L.*) was mixed with dilution (distilled water+ammonia solution (3%); +150°C; 5 MPa) at a ratio of 1:10. The prepared extagent in the tube for 120 min continued boil and cooled and filtered. The method was used to determine the amount of GA in the extract. Acetonitrile+methanol+distilled water+acetic acid (35:20:45:1) was used as an active phase (flow rate 0.5cm/min). Detection was performed at a wavelength of 256 nm (Table 2).

Table 2. GA content in *glycyrrhiza glabra L.*root extract *(n=3–5)*

Conditions of extradiction	**Identification through gravimetric method**			**Identification through HPLS**	
	Quantity in water extract (%)	Quantity in filtered content (%)	Quantity in accordance to dry plant mass (%)	Concentration in extract (mg/ml)	Share in extract content (%)
Distilled water + ammonia solution (3%); +150°S; 5 MPa	0,074±0,005	0,083±0,04	14,3±0,28	7,75±0,3	0,9±0,04

It reported that the GA content from aqueous extract is a 13.6% [32] compared to the dry plant mass, a 7.3% [37] in some data, and 0.88% in ethanol extract [35], and also when used ultra-sound, it was found to be 3.64% [36].

Synthesis and chemical identification of supramolecular complex of glycyrrhizic acid with menthol.

The supramolecular complex of GA with menthol was obtained according to Figure 2.

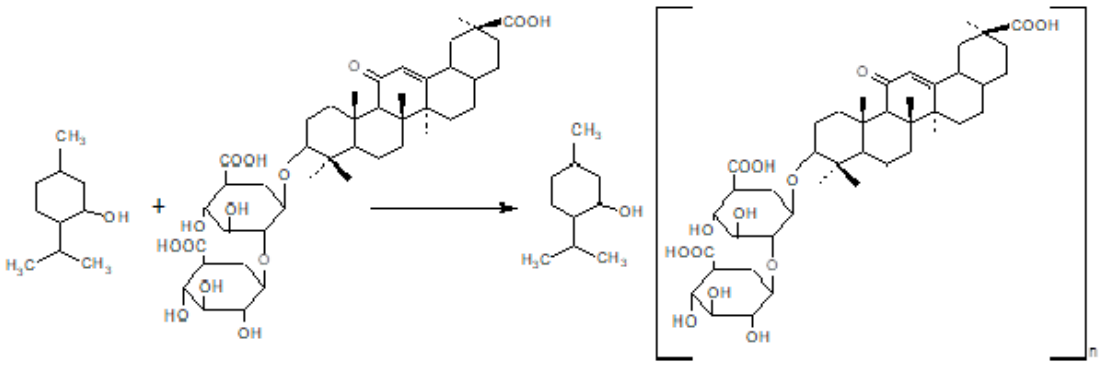

Figure 2. Reaction of the supramolecular complex between GA and menthol

Supramolecular complexes with molar ratio 2:1; 4:1; 9:1 of glycyrrhizic acid with menthol were obtained in water:acetone system.

Some physical-chemical properties of the resulting supramolecular compounds were studied and their chemical structures were investigated by IR spectroscopy (Table 3).

Table 3. Some physical-chemical descriptions of supramolecular complex of GA with menthol

№	Substances	T_{liquid}, ^0S	R_f^* (system)	Solubility	IR spectrum, cm^{-1}
1	GA:Menthol 2:1	218-220 S^0	0.8	Water Spirt	3400- 3500(OH); 2924(CH_3) 2857-(SN_2); 1637-1725-(SO) 1085-(-O-)
2	GA:Menthol 4:1	220-225 S^0	0.9	Water Spirt	3400- 3500(OH); 2924(CH_3) 2857-(SN_2); 1637-1725-(SO) 1085-(-O-)
3	GA:Menthol 9:1	228-230S^0	0.8	Water Spirt	3400- 3500(OH); 2924(CH_3) 2857-(SN_2); 1637-1725-(SO) 1085-(-O-)

As shown in Table 3, all obtained complex compounds are well soluble in water. It can be seen that the liquid temperature is between 200 and 230^0C.

System: benzene: chloroform 3:1

The structure of the supramolecular complex was studied by physical methods based on the interaction of organic molecules with electromagnetic radiation, in particular their IR spectrum (the frequency of vibration of atoms in the molecule, $\lambda = 10^{-4} - 10^{-2} см^{-1}$).

The valence vibrations of hydroxyl groups in the resulting complex compounds are observed in the 3500-3400cm^{-1} area, and the valence oscillations of the carboxyl groups in the GA are observed in the field 1725-1690cm^{-1} (Table 3).

In the IR spectrum of the supramolecular complex GA formed with menthol, asymmetric valence oscillations of the -CH_3 group were observed in 2924-2927cm^1. At the wavelength of 2857-2860 cm^{-1}, it is noted that the symmetric valence oscillations of the -CH_2- group are weak, and in the area 1085cm^{-1} there are valence oscillations of the -O- group.

Due to the absence of chromophore groups in the L-(-)- menthol molecule, no apparent absorption was observed in their UV spectra. Therefore, the IR spectra of menthol and its complex with GA were studied.

In the formation of a supramolecular compound, it was found that the host molecule contains several active bonds that form several bonds. It was noted that the host and guest geometric structure, that is, the diameter of the gap in the receptor molecule, corresponds to the radius of the substrate molecule. The complementarity feature allows the host molecule to select guests in a well-defined structure. It is worth noting that the GA molecule has a «guest-host» formation of clathrate compounds, its complexity with a number of medications used in medicine, to increase their activity and increase the treatment index by the effect of molecular capsules [39].

In the picture below, the supramolecular complex of 4:1 GA with mentolol was recorded by using «Shimadzu» IR-Fure spectrophotometer device (Japan) and «Perkin-Elmer Spectrum IR»-10.6.1 in the absorption range of 3400–3500cm^{-1} (Figure 3; Figure 4).

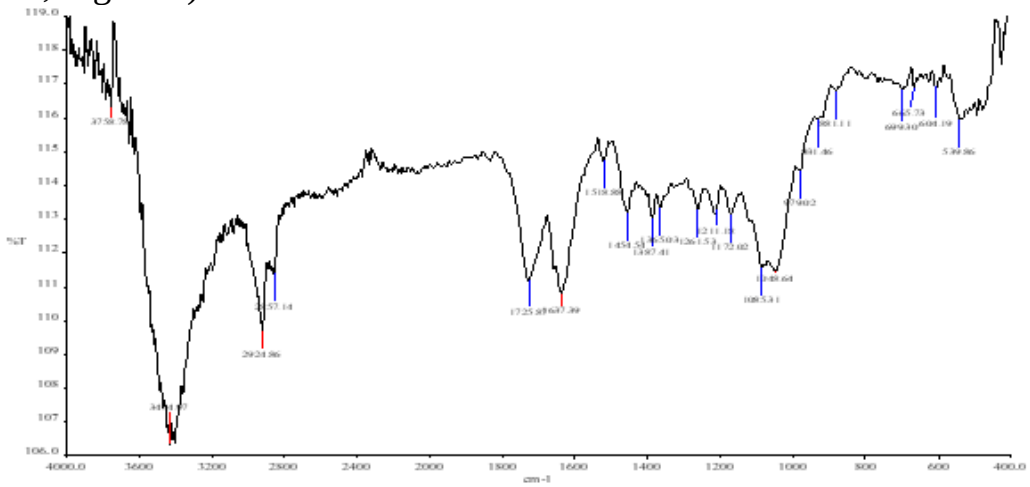

Figure 3. IR-Fure spectra of the supramolecular complex GA generated by menthol

The IR-Fure spectra were recorded using an IR-Fure spectrophotometer device (Perkin-Elmer Spectrum IR - 10.6.1; USA) in the absorption range of 3400–3500 cm^{-1}. The spectra were recorded at a resolution of >4 cm^{-1}. The vacuum conditions (0.1–0.05 mm s.u) were pressed in the form of a spectral pure KBr (“Merck”, Germany) for adsorption of moisture in the test samples.

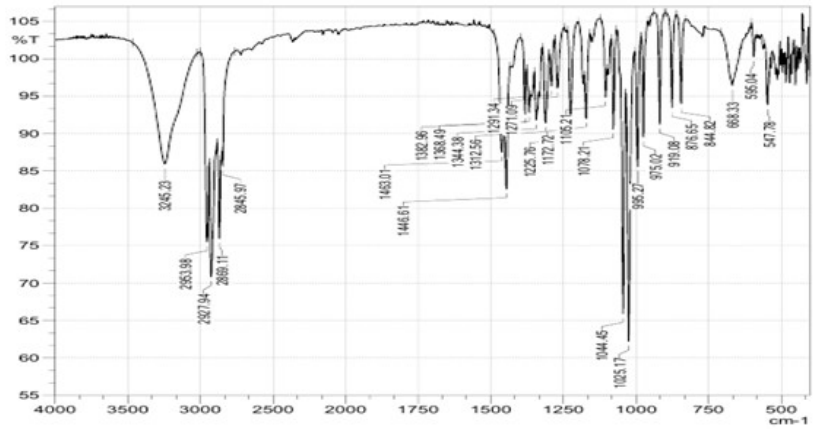

Figure 4. IR spectrum of menthol.

The IR-Fure spectra were recorded using an IR-Fure spectrophotometer device (Perkin-Elmer Spectrum IR - 10.6.1; USA) in the absorption range of 3400–3500 cm^{-1}. The spectra were determined at a resolution value of >4 cm^{-1}. The vacuum conditions (0.1–0.05 mm s.u) were pressed in the form of a spectral pure KBr (“Merck”, Germany) for adsorption of moisture in the test samples.

In this case, the shape of the oscillation is explained by the amplitude of all the atoms vibrating at the same frequency and, in turn, the change in the length of the chemical bond and the interconnection angle at normal vibrations.

If the angles between atoms change in the course of vibration, this type of oscillation is called deformation vibration. However, pure valence or pure deformation oscillations occur only in linear molecules or in highly symmetric molecules and ions (octahedrons, tetrahedrons, squares, etc.). In most multi-atom molecules and ions, mixed valence-deformation oscillations occur together, and the angles between them change as the valence bond distances change.

One of the most widely used methods for the identification of menthol with GA derived supramolecular compounds has been the use of high-performance liquid chromatography. Chromatography isoconate flow rate 1ml/min and acetylitrile : acetate buffer system was used as an eulent.

The following are the chromatographic conditions:
chromatograph- Agilent Technologies - 1200
column - Exlipce XDB - C18, 5mkm, 4.8x150mm
eluent-acetoneitrile:acetone buffer (21:89)
detector - UV (254nm)
regime-isocratic
Temperature - 25 ^{0}S
vcol-5mkl

The results showed that the amount of glycyrrhizic acid in the supramolecular complex compounds was theoretically calculated and the error rate was ±1-1.5%.

Quantitative determination was performed with respect to standard GA solution. Because the menthol molecule does not contain chromophore groups, it cannot be detected by simple spectroscopic methods. Therefore, in our experiments, we used quantitative GA to qualitatively and quantitatively determination. Quantitative computations were compared relative to the peak area at the time of the standard solution retention (Table 4).

Table 4. Results of the HPLS-based study of supramolecular complex of GA with menthol

Complexes	**Time for holding complexes in the column, min.**	**Quantity calculated from the theoretical point., mg/100ml**	**Result obtained practically mg/100ml**
GA	6.967	100.0	100.0
2:1	7.118	100.0	98.7
4:1	7.129	100.0	99.1
9:1	7.159	100.0	98.6

Initial agents for the IR-Fure spectra GA:Menthol (4:1) supramolecular

complex recorded in the experiments by using an IR-Fure spectrophotometer device (Perkin-Elmer Spectrum IR-10.6.1; USA). The correlation coefficients of functional groups in the molecules GA ($C_{42}H_{62}O_{16}$; «Biochemica», Germany) and ISK ($C_{12}H_9NO_2$; Biochemica, Germany) were 0.84 and 0.70, respectively.

It was noted that the resulting GA:Menthol (4:1) supramolecular complex is 99.1%.

As can be seen from the values presented in Table 2, the quantities of theoretically obtained complexes are consistent with the results obtained in practice, and their difference does not exceed 1.0-1.5%. This proves that the method of HPLS can be used to standardize the obtained supramolecular complex compounds. Qualitatively standard of GA hold time in the column was set as (6,5-7,0 min).

Chemical synthesis the supramolecular complexes of GA with physiologically active compounds provide lot perspectives to use in agriculture. Our near future work will be addressed to test this newly supramolecular compounds based on GA:Menthol for plant growth and (a) biotic stress resilience.

Conclusion

In the experiments, we have obtained the supramolecular complexes of glycyrrhizic acid and menthol. The resulting supramolecular complexes have the highest yields in the ratio of 4:1, and the resulting GA:Menthol (4:1) complex has been chemically identified by comparing the IR-Fure spectra of the primary agents. Initial agents of the supramolecular complex GA:Menthol (4:1) (GA ($C_{42}H_{62}O_{16}$; Biochemica, Germany) recorded using an IR-Fure spectrophotometer device (Perkin-Elmer Spectrum IR - 10.6.1; USA)) and the coefficients of functional groups in the molecules consistence of ISK ($C_{12}H_9NO_2$; Biochemica, Germany) were 0.84 and 0.70.

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