Journal of the Serbian Chemical Society
JSCS@tmf.bg.ac.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *87* (5) 629–640 (2022)
JSCS–5546
Original scientific paper
Published 16 May 2022

Antimicrobial and anticancer activities of copolymers of tri-*O*-acetyl-D-glucal and itaconic anhydride

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(Received 28 August, revised and accepted 10 December 2021)

Abstract: This paper reports the synthesis and characterization of monomers itaconic anhydride (IA) and tri-*O*-acetyl-D-glucal (TAG) as well as 4,6-di-*O*--acetyl-D-glucal (PSG). The homopolymers and copolymers of IA and TAG were synthesized *via* free radical copolymerization in bulk, using azobisisobutyronitrile as an initiator with different feed ratios of monomers. Their structural, molecular and thermal characterization was done using ^{1}H-NMR spectroscopy, gel permeation chromatography and differential scanning calorimetry, respectively. The glass transition temperature (T_g) of copolymers was found in the range of 139–145 °C. The highest T_g was found for IA–TAG2 copolymers, whereas IA–TAG4 copolymer showed lowest T_g. The molecular weight of the copolymers was in the range 5157–5499 g mol^{-1}. The monomer TAG undergoes Ferrier rearrangement in water to give PSG. The antimicrobial activity of IA, TAG, PSG and IA–TAG copolymers was studied using the minimum microbicidal concentration-broth dilution method. TAG, IA and PSG, as well as homopolymer and copolymers of IA and TAG are excellent antimicrobial agents.

Keywords: free radical polymerization; glass transition temperature; homopolymer; Ferrier rearrangement; cytotoxicity; antibacterial activity.

INTRODUCTION

The number of aggressive infections is on the rise, accompanied by an increase in the number of antibiotic resistant microorganisms. Therefore, the need to screen for novel anti-microbial compounds is imperative.[1,2] The identification of

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https://doi.org/10.2298/JSC210828108D

anti-cancer drugs is another thrust area of research. Environmental and economic concerns necessitate the use of polymer from renewable resources.[3,4] Polymers based on renewable resources such as plant and agro-industrial waste are of considerable interest as substitutes for petroleum-based materials.[5,6] Such materials are attractive from an environmental perspective, especially if they are biodegradable. In this regard, glucose or fructose can be a good source of monomers as they are available in abundance and at a low cost.[7] Tri-O-acetyl-D-glucal (TAG) and itaconic anhydride (IA) both can be obtained from renewable resources, *i.e.*, D-glucose and itaconic acid (ITA), respectively. IA is produced from the pyrolysis of citric acid or through the fermentation of carbohydrates forming ITA followed by its dehydration to form the anhydride.[8,9] IA can be polymerized or copolymerized with various other monomers by free radical reactions. IA is more reactive than maleic anhydride and is an alternative monomer for introducing polar functionality into polymers.[10–12] Polyacrylate derivatives containing IA moieties have been prepared using the microwave irradiation technique.[13] From the various heterocyclic derivatives prepared from IA precursor by Narayana *et al.*[14] good antibacterial activity was shown by 1-(4-iodophenyl)-3-methylidenepyrrolidine-2,5-dione, whereas the derivatives 1-(4-chlorophenyl)-3-methylidenepyrrolidine-2,5-dione and 3-methylidene-1-(1,3-thiazol-2-yl)pyrrolidine-2,5--dione showed promising antifungal properties. [^{18}F]2-fluoro-2-deoxy-β-D-allose ([^{18}F]2-FDβA) was synthesized from TAG in a two-step reaction and was shown to be a possible candidate as a radiotracer for breast tumour detection.[15] Han *et al*. reported the biological activity of TAG-maleic anhydride copolymer by MTT method and ID_{50}-values against tumour cells.[16] Recently antibacterial active films were prepared from poly(itaconic acid), which was functionalized with quaternized thiazole group and incorporated in gelatine and oxidized starch. These films also showed antioxidant capacity.[17]

In our study, TAG and IA were synthesized from D-glucose and ITA, respectively, and PSG was prepared from TAG. The copolymers of TAG and IA were prepared using bulk polymerization under free-radical conditions. The polymerization was carried out under nitrogen atmosphere using AIBN as an initiator at 60 °C. The copolymers were prepared using different compositions. The ratio of IA to TAG varied as follows: 9:1, 8:2, 7:3, 6:4 and 5:5. The structural characterization of the obtained copolymers was done by ^{1}H-NMR spectroscopy. Thermal and molecular characterizations were done using DSC, and GPC respectively. Here we propose the use of TAG, IA, PSG and homopolymer and copolymers of IA and TAG as potential antimicrobial as well as anticancer agents.

EXPERIMENTAL

Materials

Itaconic acid (99.0 %), phosphorus pentoxide (95.0 %), D-glucose (95.0 %), perchloric acid (98.0 %), red phosphorus (95.0 %), bromine (95.0 %), acetic acid (98.0 %), sodium

acetate (99.5 %), zinc dust (99.0 %), copper sulphate (95.5 %), azobisisobutyronitrile (AIBN) (95.0 %), silica gel (60-120 mesh) for column chromatography, were used as supplied. Chloroform (99.7 %) and acetic anhydride (98.0 %) were distilled before use. All the above chemicals were obtained from S. D. Fine Chem Limited, Mumbai, India.

Methods

FT-IR spectrum of the IA was recorded on a Shimadzu IR-Affinity-1, FT-IR spectrophotometer in the region from 4000 to 400 cm^{-1} using the KBr pellet method. The ^{1}H-NMR spectra were obtained by dissolving the samples in deuterated chloroform ($CDCl_3$) using a Brucker AV III 500 MHz FT-NMR or a Brucker DRX500 spectrometer. Chemical shifts (δ in ppm) are given relative to tetramethylsilane. Differential scanning calorimeter (DSC) was used for the melting point and to check the purity of the monomers and for determination of glass transition temperature (T_g) of polymers. DSC scans were recorded in nitrogen atmosphere at a heating rate of 10 °C /min by using 3±1 mg of powdered samples using Discovery SDT 650, TA Instruments, TGA-DSC. The molecular weight and polydispersity index of obtained copolymers were calculated using Perkin Elmer Series 200 system equipped with column: PL gel 5 microns Mixed D: 300 mm×7.5 mm using THF as mobile phase at a flow rate of 1.0 mL min^{-1} and refractive index detector.

Culture of bacterial and fungal cultures

1 % cultures of *Escherichia coli* (strain no. MTCC 2345) and *Staphylococcus aureus* (Strain no. MTCC 737) were cultured overnight at 37 °C with constant shaking in nutrient broth (HiMedia). They were sub-cultured the next morning at 1 % in nutrient broth and allowed to grow under the same culture conditions as described above for 6 h (end of log phase). *Streptococcus pyogenes* (strain no. MTCC 442) and *Pseudomonas aeruginosa* (strain no. MTCC 741) were cultured under similar conditions in Brain Heart Infusion (BHI) medium (HiMedia) while *Candida albicans* (strain no. MTCC 183) was cultured in MGYP medium (malt extract (3 mg mL^{-1}), glucose (10 mg mL^{-1}), yeast extract (3 mg mL^{-1}) and peptone (5 mg mL^{-1}), all obtained from HiMedia.

*Estimation of minimum microbicidal concentration (*MMC*)-broth dilution method*

At the end of the log phase of the cultures, the optical densities (*OD*) were estimated at a wavelength of 600 nm, and the cultures were diluted to an *OD* of 0.2. Since 1 *OD* was taken to correspond to 5×10^8 cells mL^{-1}, 20 μL of the diluted culture was added to 980 μL of twice the concentrations of the respective culture broths so that the final concentration of cells was 2×10^6 cells mL^{-1}. 100 μL of cell suspensions were then plated out in flat bottomed 96-well plates (Tarsons). 100 μL of the autoclaved test sample in different concentrations were added correspondingly. Cultures with only sterile distilled water were used as negative controls while cultures with 100 μL of commercially available antibacterial/antimycotic solution (HiMedia) containing penicillin (100 U), streptomycin (0.1 mg) and amphotericin B (0.25 μg) were used as positive controls. All cultures were performed in duplicates. The cultures were incubated for 24 h at 37 °C. The *MMC* was taken as the concentration at which no growth was observed (comparable to positive control).

Culture of A549 cell line

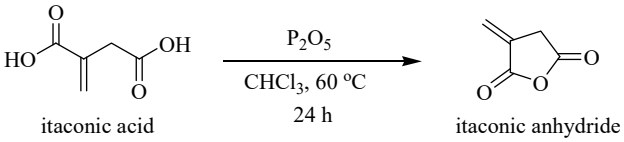
A549 human lung adenocarcinoma cell lines were cultured in Dulbecco's modified Eagle medium (DMEM containing Phenol red; HiMedia) with 10 % Foetal bovine serum (FBS; HiMedia) at 37 °C in a humidified incubator with 5 % CO_2.

Trypan blue viability assay

A549 cells of >95 % viability were plated out at a cell density of 1.5×10^5 cells mL^{-1} in a 24-well plate (Tarsons) and cultured overnight at 37 °C in a humidified incubator with 5 % CO_2. The next day, the spent medium was completely removed and equal volumes of fresh medium and autoclaved 2× concentration of polymers were added to different wells and incubated for a further 12 h and 24 h at 37 °C and 5 % CO_2. Cultures sans polymers were used as a negative control. All cultures were performed in duplicates. After the incubation period with the test compound, the cultures were examined microscopically, and cells were carefully trypsinized. The cell suspension was centrifuged at 1200 rpm for 7 min, and the cell pellet was re-suspended in 1 mL of fresh complete medium. 90 µL of the cell suspension was mixed with 10 µL of 0.4 % Trypan blue (HiMedia), incubated for about 5 min at room temperature and a manual cell count was performed using a haemocytometer.

Synthesis of itaconic anhydride

To a two-litre reaction kettle equipped with a mechanical stirrer and reflux condenser, ITA (0.75 mol) dissolved in one litre of chloroform was taken. To the solution, P_2O_5 (1.0 mol) was added. The reaction mixture was refluxed with stirring for 24 h. It was then decanted leaving a viscous brown residue at the bottom of the flask and the solution was concentrated to half by removing chloroform, using the rotary vacuum evaporator. On cooling the remaining solution to 0 °C, itaconic anhydride crystallizes out which was separated by filtration followed by drying in the oven for 2 h at 40 °C. The two crops of crystals were obtained giving white crystals of IA (yield, 90 %, m.p.: 69 °C), Scheme 1.



itaconic acid itaconic anhydride

Scheme 1. Synthesis of IA.

Synthesis of TAG

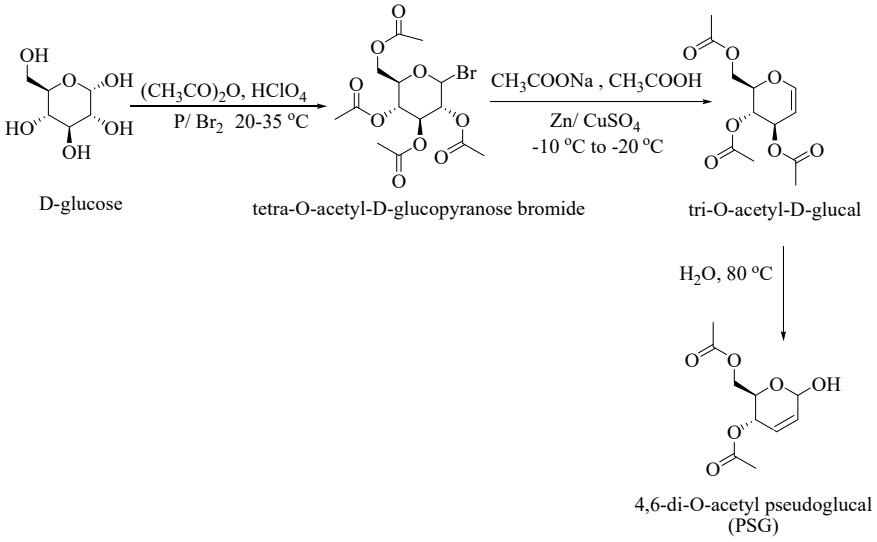
TAG was synthesized in a multistep reaction (Scheme 2). *α*-D-Glucose (0.33 mol) was added slowly to a mixture of acetic anhydride (1.96 mol) and 70 % perchloric acid (1.2 mL) at 35 °C, in a duration of 1 h with continuous stirring. After the addition of red phosphorus (0.48 mol) to the flask, it was cooled to 5 °C in an ice-salt mixture. Bromine (0.56 mol) was then added drop-wise, with continuous stirring at such a rate as to maintain the internal temperature below 20 °C. Subsequently, 15 mL of water was added during the course of 30 min with the careful control of temperature. The mixture was filtered, and the filter paper was washed with a little acetic acid. The filtrate so obtained contained tetra-*O*-acetyl-*α*-D-glucopyranose bromide. Meanwhile, a solution of sodium acetate (1.95 mol) in the water of 250 mL and glacial acetic acid 200 mL was prepared. To this solution, zinc dust (1.68 mol) along with $CuSO_4$ solution (0.04 mol in 40 mL water) was added at 5 °C. When the blue colour of $CuSO_4$ solution disappeared, the filtrate containing tetra-*O*-acetyl-*α*-D-glucopyranose bromide was added gradually in the time span of 1 h keeping the reaction temperature between –10 and –20 °C, and the stirring was continued for 3 h at the same temperature.

The obtained reaction mixture was filtered, and the filter paper was washed with 50 % acetic acid. The 500 mL water was added to the filtrate at 0 °C and the reaction mixture was extracted with chloroform. To remove the traces of water from the chloroform solution, it was

stored overnight on the bed of $CaCl_2$. The chloroform solution was decanted and evaporated under reduced pressure. The crude product was purified using column chromatography and recrystallized with petroleum ether and diethyl ether mixture (yield, 92 %, m.p.: 55 °C).

Synthesis of PSG

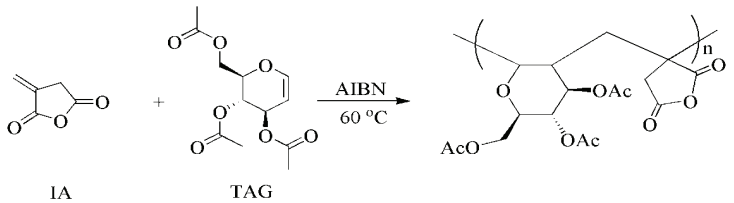
TAG (0.01 mol) was dissolved in 100 mL of water and the solution obtained was stirred at 80 °C for half an hour. It was then brought to room temperature and PSG was extracted with chloroform and concentrated using the rotary evaporator (yield, 85 %, m.p.: 125 °C), Scheme 2.



Scheme 2. Synthesis of TAG and PSG.

Synthesis of copolymers of IA–TAG

To the three-necked round bottom flasks equipped with mechanical stirrer and nitrogen atmosphere, IA and TAG were added with varying mole ratios such as 9:1, 8:2, 7:3, 6:4 and 5:5 and 1 % of AIBN. The temperature was maintained at about 60–65 °C and stirring was continued till the reaction mixture became viscous. The reaction mixture was washed with chloroform to remove the unreacted TAG and IA, and dried under vacuum at 80 °C. The copolymers so obtained are designated as IA–TAG, followed by a numerical suffix giving the moles of TAG in the monomer feed. For example, the copolymer prepared using one mole of TAG, and nine moles of IA is designated as IA–TAG1 (Scheme 3).



Scheme 3. Synthesis of IA-TAG copolymers via free radical polymerization.

Spectral data of the synthesized compounds are given in Supplementary material to this paper.

RESULTS AND DISCUSSION

TAG was obtained from D-glucose in a multistep reaction *via* acetylation and bromination, followed by reduction *in situ*, as shown in Scheme 2. TAG, upon treatment of with water at 80 °C, underwent Ferrier rearrangement to give PSG (Scheme 2). The copolymers of TAG and IA were obtained via bulk polymerization under free radical conditions. The homopolymer of IA was also prepared under similar conditions, but the homopolymer of TAG could not be obtained even after 96 h of continuous stirring.

The structural characterization of the obtained IA–TAG copolymers was done using ^{1}H-NMR spectroscopy. The ^{1}H-NMR spectrum of IA–TAG5 shown in Fig. S-5 of the Supplementary material, showed a sharp peak due to $–CH_2$ protons of IA in backbone at δ 1.8–1.9 ppm, and protons of $–CH_3$ of the acetyl group of TAG at δ 1.9–2.0 ppm, which confirmed the incorporation of the monomer of IA and TAG in the copolymer backbone. The succinic anhydride methylene group in the pendant is observed at δ 2.5 and 3.2 ppm. The presence of these peaks along with the peaks observed at δ 2.1–2.2 ppm and 3.6–3.7 ppm, due to CH bonds of TAG in the backbone, confirms the polymerization. The peaks in the region δ 4.9–5.5 ppm are due to CH groups in the pendant ring of TAG. The termination of the reaction can occur via disproportionation reaction generating vinylic groups which are observed in the region δ 5.8–6.1 ppm. The peaks are mostly broad due to the changes in the microstructure of the copolymers. This is a common phenomenon observed in ^{1}H-NMR spectra of polymers.[18]

Molecular and thermal characterization of IA–TAG copolymers

The molecular and thermal characterization of IA–TAG copolymers was done using GPC and DSC, respectively. The results are summarized in Table I. The molecular weight of IA–TAG copolymers was in the range of 5147 to 5469 g mol^{-1} and a slight increase in the molecular weight of copolymers was observed with the growth of the mole fraction of TAG in the feed, which is due to the higher molecular weight of TAG monomer. The polydispersity index of IA–TAG copolymers was found in the range of 1.7–2.1. The T_g of IA–TAG copolymers was found in the range of 133–148 °C. The DSC scans are shown in Fig. S-6 of the Supplementary material.

A marginal increase in T_g was observed with the rise of the TAG concentration in the feed and was in the order IA–TAG1 < IA–TAG2 < IA–TAG3 < < IA–TAG4 < IA–TAG5.

The rise of T_g with the increase in TAG in the feed ratio could be due to the incorporation of monomer with a bulky pendant group, but further growth of

TAG decreases the softening temperature, which may be due to lower melting point of TAG monomer.

TABLE I. Molecular weights (M_w), *PDI* and T_g of IA-TAG copolymers

Copolymer designation	Mole ratio of IA:TAG	M_w / g mol^{-1}	*PDI*	T_g / °C
IA–TAG1	9:1	5147	2.1	144
IA–TAG2	8:2	5200	2.0	202
IA–TAG3	7:3	5327	1.8	163
IA–TAG4	6:4	5436	1.8	139
IA–TAG5	5:5	5499	1.7	145

Antimicrobial and anticancer activity

The monomers (IA, TAG), PSG, poly(itaconic anhydride) (PIA) and copolymers of TAG and IA were tested for their potential as antimicrobial and anticancer agents. The *MMC* (concentration at which no cell growth was observed) of ITA, the monomers, IA and TAG, and the polymers derived from them were estimated using the broth dilution method. The *MMC* values for the 6 organisms tested against the corresponding polymers and monomers are shown in Fig. S-7 of the Supplementary material. The concentrations at which they exhibit anti--bacterial and anti-fungal activities are tabulated in Table II.

TABLE II. MMC (mg mL^{-1}) of ITA, IA, TAG and their copolymers *in vitro*

Sample designation	Microorganism				
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenes*	*C. albicans*
ITA	2	4	2	2.75	1
TAG	1.25	>5	1.25	3.75	1.25
IA	2.5	4.75	2.5	3	1
PIA	1.5	3.75	1.5	2	1.5
IA–TAG1	2.25	4.5	2.25	3	1
IA–TAG2	2	4	2	3	1.5
IA–TAG3	2	4.25	2	3	1.25
IA–TAG4	2	4.5	2	3.25	1.25
IA–TGA5	1.75	4.25	1.75	3.5	1.25
PSG	1.5	4	1.5	3	1.25

C. albicans was seen to be most sensitive (based on the number of polymers that inhibited its growth as well as the lower concentration of the polymers) while *P. aeruginosa* was seen to be most resistant. Of the test compounds ITA and IA the sensitivity of bacteria increases when a polar group, *i.e.*, anhydride in IA is changed to a more polar protic group, *i.e.*, COOH in ITA, thus increasing its hydrophilicity. A rise of sensitivity with the increase in number of polar groups was also observed for S. *Pyogenes* and C. *albicans*, which were more resistant towards TAG as compared to PSG, the latter having an OH functionality. The expansion of antibacterial properties by the introduction of hydroxyl groups

and the increased hydrophilicity have been reported for polyphosphoniums and phenolic compounds.[19–22] *E. coli* and *S. aureus* on the other hand were more sensitive towards TAG as compared to PSG, that may be due to the higher molecular weight of TAG, which negatively effects its diffusion through the bacterial cell membrane.[23]

TAG, PSG and ITA were seen to be most effective at low concentrations while IA was seen to be effective only at higher concentrations. For the given microorganisms, the antimicrobial activity of the IA–TAG copolymers was comparable to each other. The cytotoxicity of the polymers and monomers on A549 lung adenocarcinoma cell line was estimated by the Trypan blue viability assay. The viability of cells grown in the various polymers and monomers is given in Table III.

TABLE III. Viability (%) of different concentration of itaconic acid, anhydride and its polymers *in vitro*. The effect of itaconic acid, the monomers–IA and TAG and the polymers derived from them on A549 lung adenocarcinoma cell lines viability was estimated using the Tryphan blue viability assay. Data are shown as mean of three biological replicates. Statistical significance of the measurements was determined by Student's *t*-test ($^aP < 0.001$; $^bP < 0.01$ and $^cP < 0.05$). The effect of ITA, the monomers, IA and TAG, and the polymers derived from them on A549 lung adenocarcinoma cell lines viability was estimated using the Trypan blue viability assay

Sample designation	$c_{M/P}$ (concentration of monomers and polymers) / mg mL^{-1}					
	0.38		0.75		1.5	
	After 12 h	After 24 h	After 12 h	After 24 h	After 12 h	After 24 h
Itaconic acid	94.16	87.91	91.79	64.08[a]	6.12[a]	0[a]
TAG	76.76	52.95[a]	40.82[a]	36.64[a]	2.13[a]	2.7[a]
IA	96.45	91.67	92.86	88.28	83.07[c]	80.95[c]
Polyitaconic anhydride	91.49	83.83	21.25[a]	8.22[a]	9.46[a]	0[a]
IA–TAG1	93.88	82.79	93.80	78.79	68.11[a]	34.09[a]
IA–TAG2	95.24	92.28	88.79	87.11	87.5	76.5[b]
IA–TAG3	93.5	91.23	90.82	88.89	65.23[a]	28.78[a]
IA–TAG4	97.08	95.44	93.54	85.67	75[b]	20.37[a]
IA–TAG5	83.67	83.87	66.04[a]	50.67[a]	60.29[a]	22.86[a]
PSG	1.82[a]	0[a]	0[a]	0[a]	0[a]	0[a]

PSG was the most effective cytotoxic agent, whereas the monomer IA was the least effective even at higher concentrations as shown in Fig. S-8 of the Supplementary material.

These results were corroborated by the microscopic observation of the cells prior to trypsinizing them (Fig. 1). Microscopy revealed that, with increasing concentration of the test compound, the number of attached cells reduced as compared to the control wells. The amount of detachment was also seen to be different with different polymers. Further, the cultures with the most cytotoxic com-

pounds had distinct apoptotic morphology, such as discontinuous cell membrane and presence of apoptotic bodies within the cells. Panel A in Fig. 1 is illustrative of the effect of PSG after 12 and 24 h of incubation, at different concentrations, on the adhesive properties of the adherent cell line, A549 (10× objective). As can be seen, the number of cells that are detached from the culture surface increase with the concentration of the polymer. On closer observation (panel B), one can also see the cytotoxic effect of the polymer, as seen by the formation of apoptotic bodies (20× objective) on treating with IA. Similar observations were made with the other test compounds.

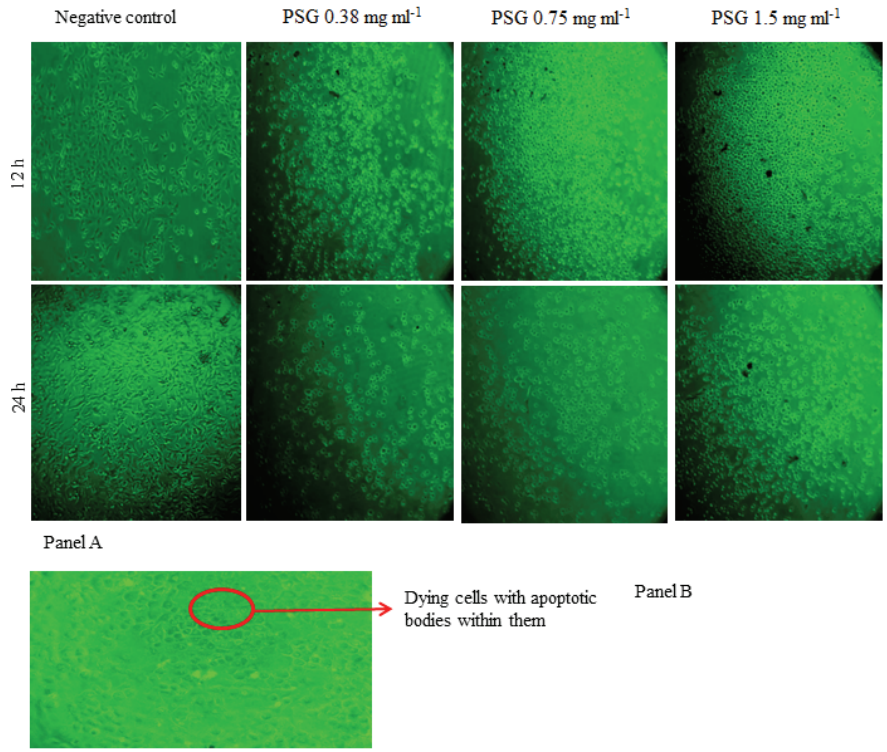


Fig. 1. Effect of ITA, IA and its copolymers with TAG on cell adhesion and morphology of A549 human lung adenocarcinoma cells.

CONCLUSIONS

In the current study, the monomers TAG and IA that were obtained from renewable resources, *i.e.*, sugar, were synthesized and characterized. The copolymers of IA and TAG were successfully synthesized using free radical polymerization conditions. Our studies reveal that the monomer, TAG, homopolymer of IA and copolymers of IA–PSG are excellent antimicrobial agents. The IA–TAG copolymers only work well as anti-fungal agents. However, at higher concen-

trations, they may be used as broad-spectrum antibiotics. Although the IA–TAG copolymers are significantly cytotoxic to A549 human lung adenocarcinoma cells, this effect is less profound than that of the base, TAG, and the homopolymer of IA. In this regard, PSG was seen to be the most cytotoxic, even at the lowest concentration tested. It can therefore be suggested that in addition to their possible use as antimicrobial agents, these sugar-based compounds may also be applied in the treatment of cancer. PSG is of particular interest and requires further studies to prove its proposed uses.

NOMENCLATURE

AIBN	Azobisisobutyronitrile
DMEM	Dulbecco's modified eagle medium
DSC	Differential scanning calorimeter
FBS	Foetal bovine serum
FT-IR	Fourier transform infrared spectroscopy
GPC	Gel permeation chromatography
IA	Itaconic anhydride
ITA	Itaconic acid
PIA	Poly(itaconic anhydride)
MMC	Minimum microbicidal concentration
NMR	Nuclear magnetic resonance
OD	Optical density
PSG	4,6-Di-*O*-acetyl pseudoglucal
TAG	Tri-*O*-acetyl-D-glucal
THF	Tetrahydrofuran
TMS	Trimethylsilyl

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/11108, or from the corresponding author on request.

Acknowledgements. CD, HS and RC are thankful to SICART-CVM Gujarat for GPC analysis, IISc Bangalore for ^{1}H NMR, and Department of Chemical Engineering, BITS Pilani K K Birla Goa Campus for DSC.

ИЗВОД

АНТИМИКРОБНА И АНТИКАНЦЕРОГЕНА АКТИВНОСТ КОПОЛИМЕРА ТРИ-*O*-АЦЕТИЛ-D-ГЛУКАЛА И АНХИДРИДА ИТАКОНСКЕ КИСЕЛИНЕ

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У раду је приказана синтеза и карактеризација мономера анхидрида итаконске киселине (IA) и три-*O*-ацетил-D-глукала (TAG) као и 4,6-ди-*O*-ацетил-D-глукала (PSG).

Хомополимери и кополимери IA и TAG синтетизовани су кополимеризацијом преко слободних радикала у маси коришћењем азо-бис-исобутиронитрила као иницијатора и са различитим односима мономера. Полимери су карактерисани у погледу структуре, грађе молекула и термичких својствава медодама ^{1}H-NMR спектроскопије, гел-пермеабилне хроматографије и диференцијалне скенирајуће калориметрије. Температура стакластог прелаза (T_g) кополимера је у опсегу од 139–145 °C. Највећи T_g су имали IA––TAG2 кополимери, док је IA–TAG4 кополимер показао најнижи T_g. Моларна маса кополимера била је у опсегу 5157–5499 g mol^{-1}. Мономер TAG подлеже Феријеовом преуређењу у води и даје PSG. Антимикробна активност IA, TAG, PSG и IA–TAG кополимера је проучавана методом разблаживања минималне микробицидне концентрације у хранљивом медијуму. TAG, IA и PSG, као и хомополимери и кополимери IA и TAG, одлични су антимикробни агенси.

(Примљено 28. августа, ревидирано и прихваћено 10. децембра 2021)

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