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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SODIUM SALT BASED PRESERVATIVE

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Abstract
In this study, sodium salts were derived from natural phenolic acids and employed as preservatives. The synthesized sodium salts were characterized by FTIR, 13CNMR and 1HNMR. The synthesized derivatives were further evaluated to analyze their potential for antimicrobial activities, anti-oxidative potential and preservation efficiency. The reports revealed outstanding preservative potential and could be used as a substitute to replace existing preservatives. The derivatives which are reported in this work can be employed for further understanding their potential to be used for food and pharma industries. These innovative compounds can be used as a substitute to existing preservative. These in addition to preservation can impart anti-oxidant properties to the product.
Keywords: Sodium salts; Phenolic acids; Anti-microbial activity; Antioxidant; Preservation efficiency.

1. Introduction

Natural phenolic acids are available in different parts of the plants mostly in form of glyosidic conjugates, amides, and esters. Phenolic acids are basically secondary metabolites of plants and are present in cell walls of plants [1]. These complexes are mostly the essential part of food. These phenolic compounds have outstanding performance in terms of anti-bacteria, anti-inflammation, anti-oxidation, anti-viral, anti-carcinogenic, anti-atherogenic, anti-hypertensive, anti-tumor and the like [2]–[4]. Extracting these phenolic compounds can greatly benefit innovations and advancements in sectors such as medicines, food, beauty products etc [5]. The method which is used from extraction of phenolic compounds from plants is known as alkaline hydrolysis [6]. Much research advancement has been focused on extraction of phenolic compounds from plants and using them for various applications. Phenols have certain biological properties that can be understood by studying the molecular structure (hydroxyl or methoxyl groups), carboxylic groups, benzene rings [5], [7]–[10]. The derivatives of phenolic acid are usually isolated and blended as extract of plants for uses in diverse application. Forming of stable phenoxy radicals are dedicated to the manifestation of side chains conjugates and nucleus of phenolic acids that results in formation of stable radicals when exposed to UV absorption [7], [11], [12]. Therefore, the ability is further enhanced for terminating reactions related to free radical formation. As a result of this ability they are capable of suppressing oxidation reactions that are induced on radiation and have outstanding free radical scavenging

ability [13]–[16]. Also these phenolic acids can be employed for protection of physiological cell integrity. The phenolic acids have photo-protective ability due to which they are incorporated into cosmetic creams and lotions. Phenolic acids, when added into food products acts as preservatives and aids in increasing the shelf life of foods by inhibiting the peroxidation of lipids and prevents spoilage due to oxidation [1], [6][1], [6], [13]. In the similar way phenolic acids act as protection against numerous diseases.

Biological properties of the alky groups are evaluated and are largely employed for applications such as preservatives against microbial activities in beverages, food, medicines and cosmetics [11]. The activities of phenolic derivatives were seen to have very low toxicity, this values increases with increase in the length of the alkyl chain. The ester of butyl is more toxic in comparison to the ester of methyl ester. Literature of the relation between molecular structure of compound and its antioxidant activity has been analyzed. Monophenols are reported to be less effective in comparison to polyphenols. Also, it is considered that the second group of hydroxyl when attached at para or ortho positions will enhance the anti-oxidant activities [15]. Herein, we have reported the synthesis of sodium derivative of phenolic acids by neutralization of phenolic acid by NaOH. The activities of the derived sodium salts such as anti-microbial activity, anti-oxidative activity were evaluated. Various bacterial strains, yeasts and fungus were used to study the antimicrobial activity. Also the potential of these derivatives to be employed as preservatives were evaluated and reported.

2. Materials and Methods

2.1 Materials

The chemicals that were required for synthesizing sodium derivatives from phenolic acid and evaluating their anti-microbial activity, anti-oxidant activity, and efficiency of preservation was procured from CDH ltd, and Loba Chemicals. For carrying out thin layer chromatography (TLC) the silica gel plates were coated. Solvents which was used for extraction was Hexane and Ethyl acetate.

2.2 Derivation of salts from phenolic acids

Cells of plant possess phenolic acids which are integrated and these will be released upon alkali hydrolysis. Sodium salts of naturally occurring phenolic acids viz. cinnamic acid and benzoic acid can be obtained by the neutralization of phenolic acid with NaOH.

2.3 Evaluating the anti-microbial activity

The antimicrobial activities of the derivatives of phenolic acid were evaluated against bacteria, fungi and yeast. The minimum inhibition concentration (MIC) was measured to understand the antimicrobial activity. MIC can be defined as the least concentration of phenolic acid derivatives that could resist the microbial growth. The anti-microbial activity was observed on petri dishes. The growth of culture was carried out at temperatures that correspond to aerobic atmosphere for time period varying from 20 to 120 hr. The cultures of bacteria that were employed for the experimentation was prepared in broth containing nutrients. The cultures of yeast and fungi were done in malt extract. Initially the density of bacteria was around 107 CFU/ml. In every petri dish, suspension of micro-organism (50 µl) was added to nutrient broth (200 µl) which contains phenolic acid derivatives. Dilution of antimicrobial agent was done by using ethanol (30%). The end concentration of ethanol in the flask containing broth was maintained below 2.5% as this concentration does not alter the micro-organism growth. A

control sample was also prepared without addition of the microbial strain for comparison and evaluation. All the experiments were performed in triplets for accuracy. The results that are obtained as mean values of standard deviation. All the statistical analyses were maintained with P value of 0.05.

3. Characterization

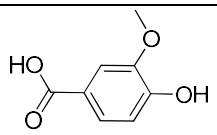
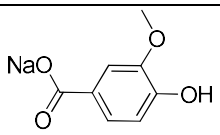
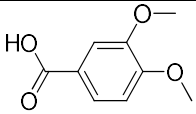
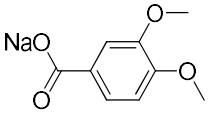
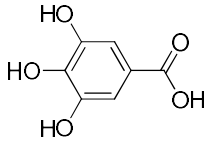
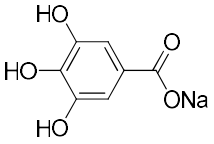
The alkali salts that were synthesized as preservatives were characterized by spectral means FTIR, 1HNMR, 13CNMR, mass spectroscopy and elemental analysis. The infrared spectra (IR) was carried out using KBr pellets method on Perkin Elmer spectrum II. The characterization of 13C NMR and 1H NMR spectra was analyzed by CDCl3, and DMSO. The separation was done at 400 MHz by using standard, tetramethylsilane and performed on Bruker Advance II 400 NMR spectrometer. The measurements of chemical shifts were recorded in ppm and the coupling constants (J) was recorded in Hertz (Hz).

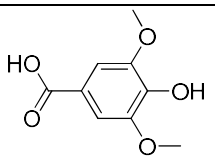
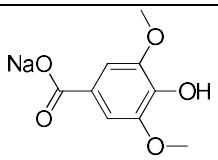
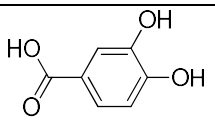
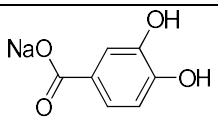
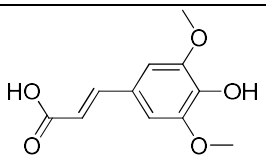
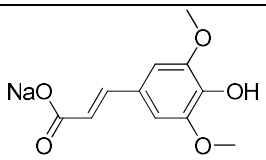
4. Results and discussions

4.1 Chemistry

Sodium salts of naturally occurring phenolic acids viz. cinnamic acid and benzoic acid were obtained by the neutralization of phenolic acid with NaOH. Table 1 shows structure of synthesized alkali derivatives.

Table 1: Structures of synthesised Alkali derivatives

S.No.	Compound(s)	Sodium salt of compound(s)
1.	 **Vanillic acid**	
2.	 **Veratric acid**	
3.	 **Gallic acid**	

4.	 **Syringic acid**	
5.	 **Protocatchuic acid**	
6.	 **Sinapic acid**	

Sodium vanilate: IR (KBR pellets) cm^{-1}; 1737 (C=O str., ester), 3368 (OH str. Phenol), 1053 (C-O-C str., -OCH3), 2345 (C-H str., OCH3), 1489 (C=C str., aromatic), 1H NMR (400 MHz, DMSO-d6) δ: 7.32 (m, 3H, ArH), 4.81 (s, 1H, OH of phenolic hydroxyl), 4.63 (s, 3H, OCH3)

Sodium veratrate: IR (KBR pellets) cm^{-1}; 1738 (C=O str., ester), 1057 (C-O-C str., -OCH3), 2904 (C-H str., OCH3), 1287 (C=C str., aromatic) 1H NMR (400 MHz, DMSO-d6) δ: 8.28 (m, 3H, ArH),) 3.49 (s, 3H, -OCH3)

Sodium gallate: IR (KBR pellets) cm^{-1}; 1732 (C=O str., ester), 3347 (OH str. Phenol), 1257 (C-O-C str., -OCH3), 2928 (C-H str., OCH3), 1376 (C=C str., aromatic)1H NMR (400 MHz, DMSO-d6) δ: 6.96 (m, 3H, ArH), 4.84(s, 1H, OH of phenolic hydroxyl)

Sodium syringate: IR (KBR pellets) cm^{-1}; 1686 (C=O str., ester), 3349 (OH str., phenol 1339 (C=C str., aromatic), 3125 (C-H str., OCH3)1H NMR (400 MHz, DMSO-d6) δ: 8.38 (m, 3H, ArH), 4.86(s, 1H, OH of phenolic hydroxyl), 4.60 (s, 3H, -OCH3)

Sodium protochatechuiate: IR (KBR pellets) cm^{-1}; 1635 (C=O str., ester), 3349 (OH str. Phenol), 1346 (C=C str., aromatic)1H NMR (400 MHz, DMSO-d6) δ: 7.9 (m, 3H, ArH), 4.70 (s, 1H, OH of phenolic hydroxyl)

Sodium sinapate: IR (KBR pellets) cm^{-1}; : 1634 (C=O str., ester), 3369 (OH str. Phenol), 1194 (C-O-C str., -OCH3), 2975(C-H str., OCH3), 1432(C=C str., aromatic)1H NMR (400

MHz, DMSO-d6) δ: : 8.23 (m, 3H, ArH), 4.65 (s, 1H, OH of phenolic hydroxyl), 3.85 (s, 3H, OCH3)

4.2 Antimicrobial evaluation of the synthesized alkali salts of natural acids:

The synthesized chitosan derivatives were tested for antimicrobial susceptibility using tube dilution method against gram-positive (S. aureus), gram-negative (K. pneumoniae, E. coli, P. mirabilis and P. aeruginosa) and fungal stains (A. niger and C. albicans). Stock standards of antibiotics and standard preservatives viz. sstreptomycin, ciprofloxacin, ampicillin, fluconazole, sodium benzoate, methyl paraben and propyl paraben were obtained as gift samples from pharmaceutical companies. The synthesized esters were dissolved in dimethyl sulfoxide (DMSO) to a concentration of 100 µg/mL, which was further diluted to get the concentrations of 50, 25, 12.5, 6.25, 3.125 and 1.562 µg/mL.

For antibacterial study double strength nutrient broth media I.P. was used and Sabouraud dextrose broth media I.P. was used for antifungal study. The test tubes were examined after 24 hours of incubation at 37±1oC for bacterial stains and after 2 days of incubation at 25±1oC for C. albicans and after 7 days of incubation for A.niger.

The tubes were scanned for any visible turbidity or sediment and tubes with no visible growth at least amount of test compound were reported as MIC (Minimal Inhibitory Concentration) Table 8 and Fig. 1.

The in vitro antimicrobial evaluation of the synthesized alkali salts showed excellent activity against bacterial and fungal species, among the synthesised alkali salts Sodium caffate, were found to be most active antimicrobial agents against E.coli. (MIC = 6.25 µM). Sodium gallate was found most active antimicrobial agents against K. pneumonia (MIC = 6.25 µM), Sodium syringate was the most effective antimicrobial against S. aeurus. Antifungal results indicated that Sodium sinapate (MIC = 12.5 µM) exhibited better activity against A. niger. The antibacterial results were compared to ciprofloxacin, Streptomycin and fluconazole is used as antifungal standard drug.

Table 2: MIC of sodium salts of natural acids

S.No.	**Compound(s)**	***K. Pneumonia***	***E.coli***	***P. mirabilis***	***S. Aureus***	***P. aeruginosa***	***C. albicans***	***A. niger***
1.	Sodium vanilate	12.5	25	25	25	25	50	50
2.	Sodium veratrate	12.5	12.5	25	50	50	25	25
3.	Sodium gallate	**6.25**	12.5	12.5	25	12.5	50	25
4.	Sodium syringate	25	12.5	25	**6.25**	25	50	25

5.	Sodium protocatechuate	25	25	50	25	50	50	12.5
6.	Sodium sinapate	12.5	25	25	25	50	25	**12.5**
7.	Sodium ferulate	12.5	12.5	25	50	25	25	25
8.	Sodium *p*-coumarate	25	25	25	25	25	50	25
9.	Sodium gentisate	25	25	12.5	25	50	25	50
10.	Sodium caffeate	12.5	**6.25**	12.5	25	50	50	25
11.	Sodium anisate	25	12.5	12.5	25	50	25	50
12.	**Streptomycin**	**6.25**	**50.0**	**25.0**	**50.0**	**6.25**	**--**	**--**
13.	**Ciprofloxacin**	**3.12**	**25.0**	**12.5**	**25.0**	**12.5**	**--**	**--**
14.	**Ampicillin**	**3.12**	**25.0**	**50.0**	**50.0**	**6.25**	**--**	**--**
15.	**Fluconazole**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**25.0**	**12.5**
16.	**Sod. Benzoate**	**25**	**25**	**25**	**25**	**25**	**50**	**50**
17.	**Methyl paraben**	**50**	**12.5**	**6.25**	**50**	**25**	**50**	**25**
18.	**Propyl paraben**	**50**	**12.5**	**6.25**	**25**	**50**	**50**	**50**

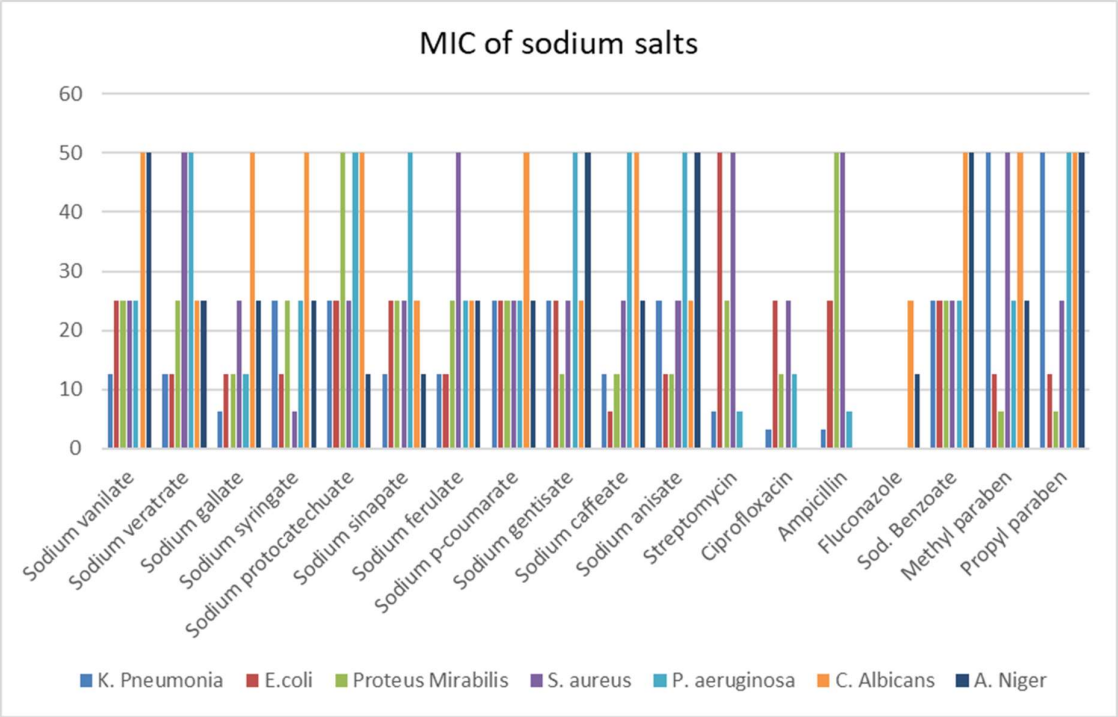


Fig 1 - MIC of synthesized sodium salts

4.3 Antioxidant activity:

Antioxidant potential of all the synthesized derivatives were evaluated by DPPH radical scavenging assay method and result were summarized in Table 2. Further, the results revealed that the compound P3 (IC50 value 6.09±0.001µM) and P10 (IC50 value 06.48 ± 0.042µM) were found more potent antioxidants than reference l-ascorbic acid (IC50 value 8.5.18±0.009 µM).Compound S3 also showed comparable antioxidant potential to reference with IC50 values as 08.39 ± 0.007 µM. Due to presence of hydroxyl group at meta position where hydroxyl group act as electron withdrawing thus facilitates hydrogen release from acid derivatives. While compound S5 (IC50 value 18.80 ± 0.003µM) and P5 (IC50 value 19.19 ± 0.021µM) exhibited lowest antioxidant activity because of the presence of hydroxyl group at adjacent positions on the phenolic ring the adjacent arrangement leads to stabilization of molecule against release of hydrogen ion.

Table 2 DPPH radical scavenging activity of synthesized derivatives

Compound(s)	IC_{50} (µM)[a]
S1	09.19 ± 0.001
S2	11.94 ± 0.025
S3	8.39 ± 0.007
S4	11.22 ± 0.012
S5	18.80 ± 0.003

S6	15.37 ± 0.054
S7	8.5.18 ± 0.009
S8	12.95 ± 0.031
S9	11.94 ± 0.025
S10	09.09 ± 0.042
S11	11.22 ± 0.012
Ascorbic acid	8.5 ± 0.009

a Value are expressed as mean ± SEM, n = 3

4.4 Preservative efficacy

4.4.1 Criteria of acceptance for preservative system:

Selected Synthesized compounds were tested for their preservative efficacy and E. coli, P. aeruginosa, S. aureus, C. albicans and A. niger were used as challenge microorganisms. The results were noted on 14th and 28th day.

A pulp based slurry of cellulose was used to evaluate the preservative effectiveness of synthesized compounds. As per USP 2004 criteria to pass the preservative efficacy test for the category of test compounds preservative effectiveness is met when there is not less than 2.0 log reduction in bacteria from the initial level at 14th day and no increase at 28th day from second week with no further increase, if value is not more than 0.5 log10 higher than the previous value, it was considered as no increase[17]. The results have been shown in **Table 3, Table 4, Table 5, Table 6, Table 7 and Fig 3, Fig 4, Fig 5, Fig 6, Fig 7.**

Table 3: Preservative effectiveness of synthesized compounds against E. coli (Log10 CFU/mL)

Compound(s)	**Zero time (CFU/ml)**	**14 days (CFU/mL)**	**28 days (CFU/mL)**
Sodium gallate	$1x10^5$-$1x10^6$	2.25	2.3
Sodium caffate		1.99	1.96
Sodium syringate		2.09	2.11
Sodium benzoate		2.20	2.33

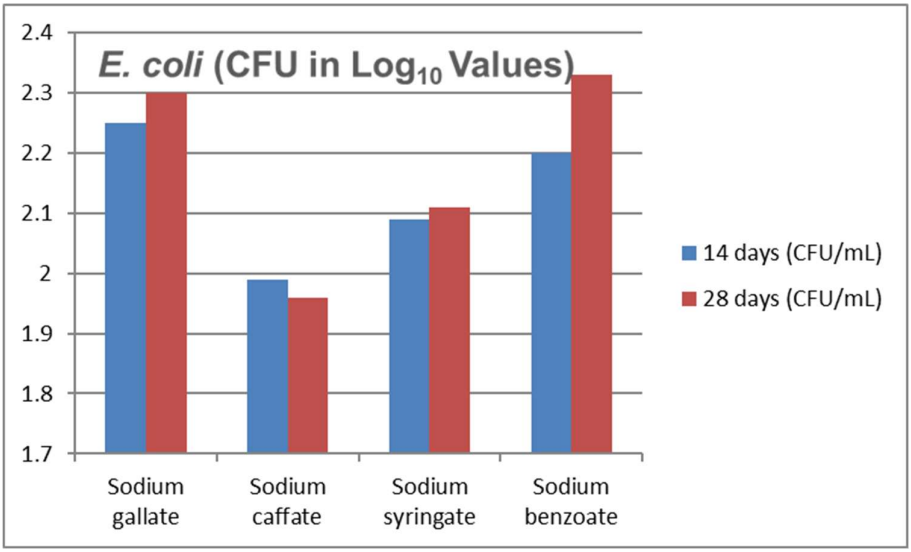


Fig 3: CFU in Log10 Values against E. coli

Table 4: Preservative effectiveness of synthesized compounds against P. aeruginosa (Log10 CFU/mL)

Compound	Zero time (CFU/ml)	14 days (CFU/mL)	28 days (CFU/mL)
Sodium gallate	$1x10^5$-$1x10^6$	2.11	2.25
Sodium caffate		2.11	2.00
Sodium syringate		2.04	2.14
Sodium Benzoate		2.30	2.20

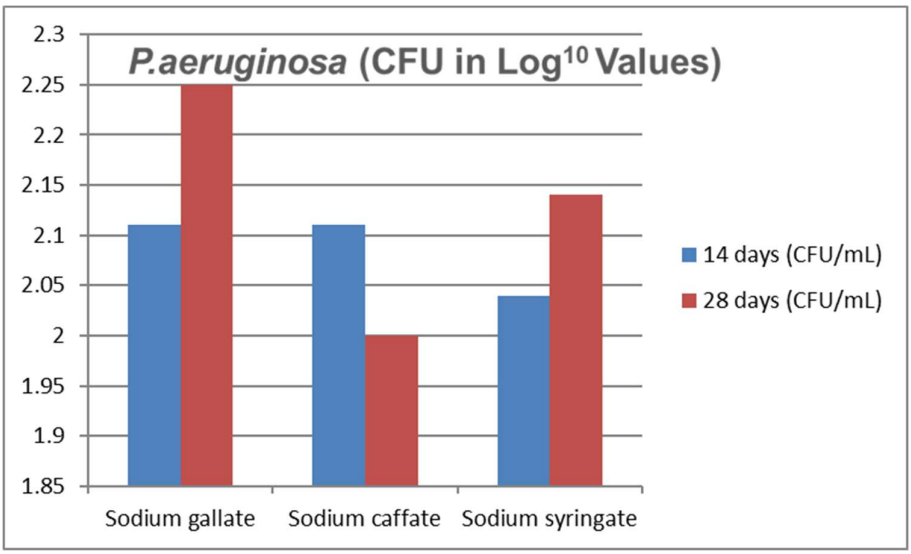


Fig 4: Log10 CFU/mL against P. aeruginosa

Table 5: Preservative effectiveness of synthesized compounds against S. aureus (Log10 CFU/mL)

Compound	Zero time (CFU/ml)	14 days (CFU/ml)	28 days (CFU/ml)
Sodium gallate	$1x10^5$-$1x10^6$	2.25	2.43
Sodium caffate		2.03	1.96
Sodium syringate		2.03	2.12
Sodium Benzoate		2.90	2.53

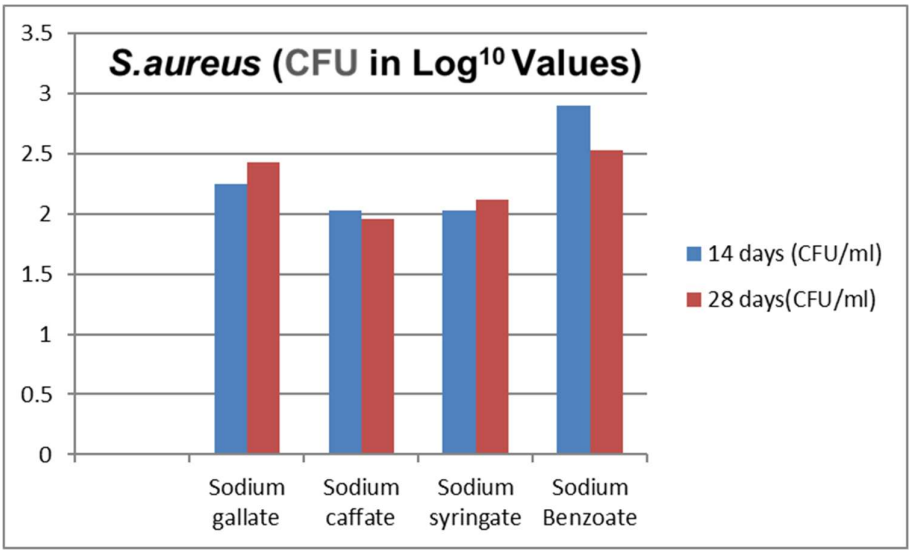


Fig 5: Log10 CFU/mL against S. aureus

Table 6- Preservative effectiveness of synthesized compounds against C.albicans (Log10 CFU/mL)

Compound	Zero time (CFU/ml)	14 days (CFU/ml)	28 days (CFU/ml)
Sodium gallate	$1x10^5$-$1x10^6$	2.36	2.50
Sodium caffate		2.23	1.90
Sodium syringate		1.99	2.07
Sodium Benzoate		2.50	2.60

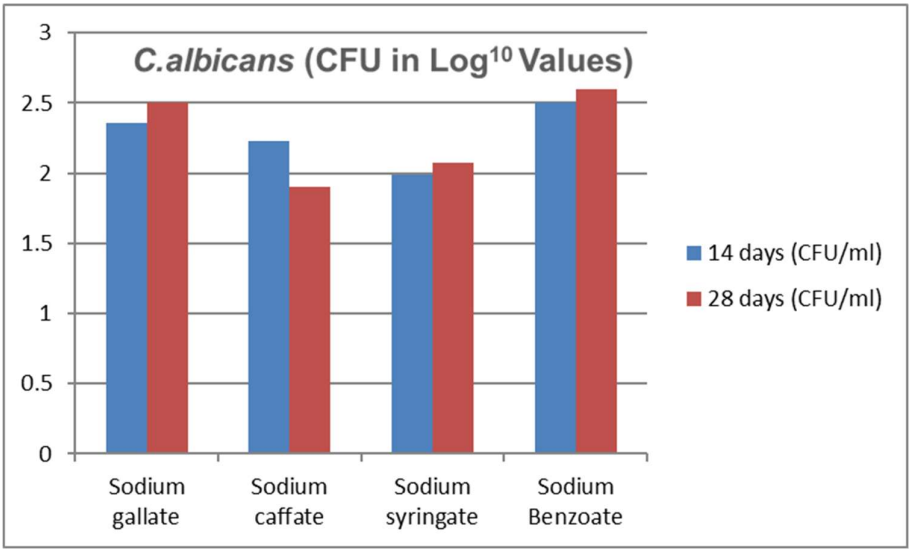


Fig 6: Log10 CFU/mL against C. albicans

Table 7-Preservative effectiveness of synthesized compounds against A. niger (Log10 CFU/mL)

Compound	Zero time (CFU/ml)	14 days (CFU/ml)	28 days (CFU/ml)
Sodium gallate	$1x10^5$-$1x10^6$	2.60	2.50
Sodium caffate		2.43	2.43
Sodium syringate		2.23	2.16
Sodium Benzoate		2.30	2.81

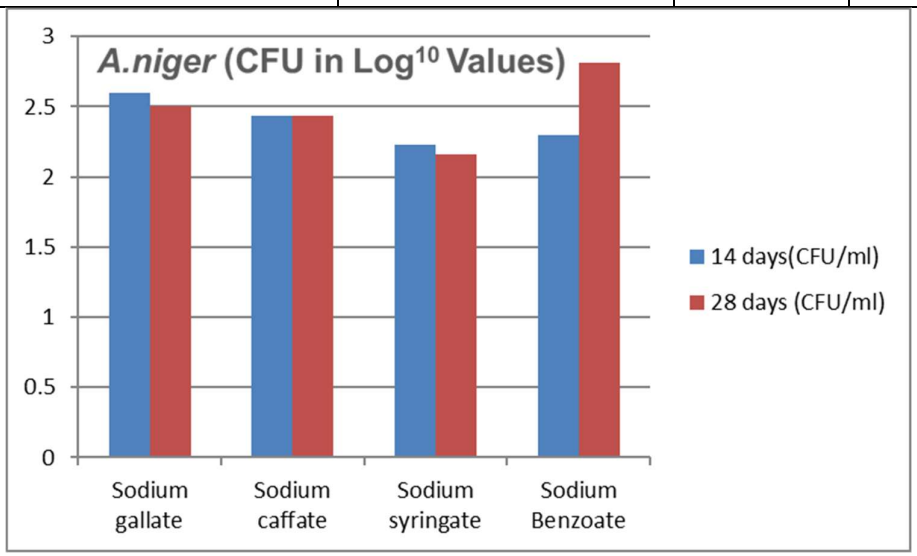


Fig 7: Log10 CFU/mL against A. niger

5. Conclusions

This study has focused on the derivatives of phenolic's which has outstanding preserving characteristics. The derived compounds were investigated to understand their antimicrobial, antioxidant and preservative efficiencies.

The studies on understanding the antimicrobial activity of synthesized alkali salts showed excellent activity against bacterial and fungal species. Mostly, with increase in the length of alkyl chain, the antimicrobial activity is seen to increase. The alkali salts that were synthesized such as Sodium caffate, Sodium gallate, Sodium syringate and Sodium sinapate had great MIC activity against E.coli, K. pneumonia, S. aeurus and A. niger respectively. The antibacterial results were compared to ciprofloxacin, Streptomycin and fluconazole is used as antifungal standard drug.

The studies on understanding the preservative efficiency revealed the sodium derivatives had great preservation potential and the results were comparable to the standard preservatives viz. streptomycin, ciprofloxacin, ampicillin, fluconazole, sodium benzoate, methyl paraben and propyl paraben.

In conclusion, the derivatives which are reported in this work can be employed for further understanding their potential to be used for food and pharma industries. These innovative compounds can be used as a substitute to existing preservative. These in addition to preservation can impart anti-oxidant properties to the product.

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