

Antioxidant and Antiparkinson Activity of Gallic Acid Derivatives

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Summary

Derivatives of gallic acid such as methyl, ethyl, propyl, butyl, octyl, and lauryl gallate are used as antioxidants in food products to scavenge reactive oxygen species. There are contradictory reports on involvement of dopamine D₂ receptors in the antioxidant activity of several agents. In the present study we synthesized gallic acid derivatives such as methyl, propyl, butyl, pentyl, isopentyl, phenyl gallate, 3, 4, 5 triacetoxycallic acid, 3, 4, 5-trimethoxy gallic acid, and methyl 3, 4, 5-trimethoxy gallic acid and assessed the free radical scavenging activity and ability of these derivatives in inhibition of haloperidol-induced catalepsy and tacrine-induced vacuous chewing movements as animal models suggestive of dopaminergic agents. Gallic acid was found to have highest free radical scavenging ability and the triacetoxycallic acid was found to have lowest free radical scavenging ability. The observations of the present study indicated that compounds with high antioxidant activity and appropriate hydrophobicity are more effective in preventing tacrine-induced vacuous chewing movements and haloperidol-induced catalepsy.

Key words: Gallic acid, esterification, antioxidant activity, Dopamine D₂ receptor

Introduction

Derivatives of Gallic acid (GA) have potential biological activities like antibacterial, antimicrobial, antifungal, etc. Numerous derivatives of GA are reported as anticancer agents, HIV-1 integrase and HIV-1RT inhibitors, and antioxidants (1- 5). Thomas *et al.*, (6) have found that antioxidant action of 7-nitroindazole contributes to its neuroprotective effect. Le and Jankovic (7) have reviewed the neuroprotective role of dopamine receptor agonists in Parkinson's disease. Chen (8) has emphasized the role of antioxidants in neuroprotection in Parkinson's disease. However, there are contradictory reports on the involvement of dopamine D₂ receptor activation in neuroprotective effect of antioxidants. Le *et al.*, (9) have reported that neuroprotection offered by the dopamine agonist and antioxidant pramipexole is independent of dopamine receptor activation. Whereas, Lida *et al.*, (10) have reported that ropinirole, a dopamine agonist, has neuroprotective effect mediated via dopamine D₂ receptor.

Packer et al., (11) have shown that α -lipoic acid, which is a low molecular weight, has antioxidant and neuroprotective activity. Di Stefano et al., (12) have assessed antioxidant activity of multifunctional codrugs of α -lipoic acid with L-dihydroxyphenyl alanine (L-dopa). Gallic acid is a low molecular weight antioxidant. Zhongbing et al., (13) studied the structure activity relationship analysis of antioxidant ability and neuroprotective effect of gallic acid derivatives and found that the neuroprotective effect depends on both their antioxidant capabilities and hydrophobicity. They concluded that compounds with high antioxidant activity and appropriate hydrophobicity were more effective in preventing the injury of oxidative stress in neurodegenerative diseases. Since GA derivatives have to be transported to the reaction sites, hydrophobicity may be an important parameter in enabling the antioxidant to reach the reaction site and to scavenge the free radicals. GA and its derivatives are widely present in the plant kingdom and represents natural antioxidants. They are present in the forms of either methylated gallic acid (e.g. syringic acid) or galloyl conjugates of catechin derivatives. They are inevitable component of the food and beverages of plant origin, such as tea Von Gadow et al., (14). There are reports that antioxidants inhibit haloperidol-induced catalepsy, a behavior mediated via dopamine D₂ receptors. All antiparkinsonian agents inhibit tacrine-induced vacuous chewing movements in rats. The present study was conducted to synthesize GA derivatives and to assess free radical scavenging activity, dopamine receptor mediated behavior and antiparkinson activity.

Material and Methods

Chemicals and drugs

All chemicals used in this study were of analytical grade and purchased from Modern scientifics, Nashik, tacrine was purchased from sigma (USA), whereas, haloperidol (Serenace inj) was purchased from medical shop.

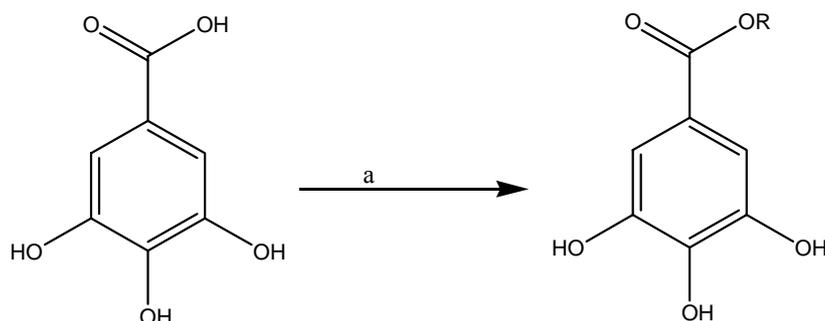
Animals

Male Wistar rats were obtained from National Toxicology Centre, Pune. The animals were housed under standard laboratory conditions, maintained on a 12 h light and dark cycle and had free access to food and water. Each animal was used only once in the experiments. All the experimental procedures and protocols used in this study were approved by the Institutional Animal Ethics Committee (IAEC) of M.G.V'S Pharmacy College, Panchavati, Nashik, constituted under the provisions of Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India. Ethical guidelines were strictly followed during all the experiments.

Synthesis of Gallic acid derivatives

The gallic acid derivatives were synthesized as described by Savi et al., (15). Gallic acid (0.1mol) and corresponding aliphatic alcohol (0.5mol) were placed in round bottom flask (RBF), the mixture was warmed slightly to dissolve the gallic acid then Conc. H₂SO₄ (0.01mol) was added as a catalyst. Toluene (30ml) was added to this mixture and the reaction mixture was refluxed for 8-10 hrs. The azeotropic mixture was separated using Dean-Stark apparatus. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled. It was then neutralized with sodium bicarbonate solution (10%) as shown in the scheme 1a. The precipitated solid was filtered immediately and dried. The crude product was then recrystallized from boiling water. Formations of esters were conformed by IR spectra which have shown absence of

COOH stretch. The compounds were also confirmed by melting point (m.p.), thin layer chromatography (TLC), and gas chromatography-mass spectrometry (GC-MS).

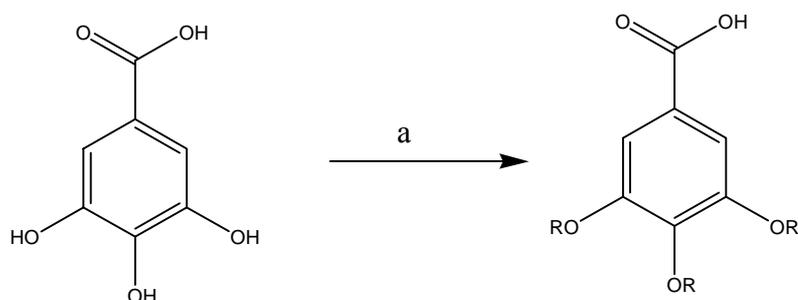


Scheme 1: (a) Conc.H₂SO₄, Toluene, Reflux

Using this scheme we prepared methyl gallate (MG), ethyl gallate (EG), Propyl gallate (PG), butyl gallate (BG), and phenyl gallate (PhG).

Preparation of 3, 4, 5 Tri acetoxybenzoic Acid (16)

3,4,5 trihydroxybenzoic acid (5.0 g, 0.02mol) and 7.5g (0.07mol) of redistilled acetic anhydride were placed in RBF to this 4-6 drops of conc.H₂SO₄ were added, the contents of the flask were swirled in order to ensure thorough mixing. It was warmed on a water bath to about 50-60⁰C for 20-25 min. The reaction mixture was allowed cool and stirred occasionally during cooling. Then 30-40 ml of water was added and product obtained was filtered at pump (Scheme 2). The triacetoxybenzoic acid (TABA) was recrystallized from ethanol. Formations of compounds were conformed by IR spectra which have shown absence of COOH stretch. The compounds were also confirmed by melting point (m.p.), thin layer chromatography (TLC), and gas chromatography-mass spectrometry (GC-MS).



Scheme 2- (a) acetic anhydride, Conc.H₂SO₄ R- COCH₃

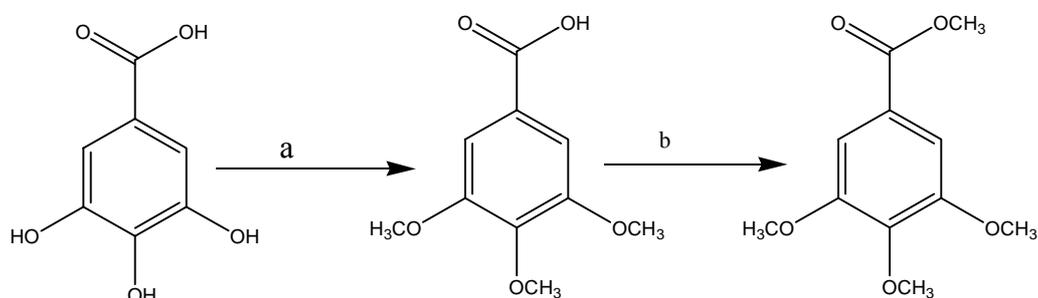
Synthesis of 3, 4, 5 Trimethoxybenzoic acid (16)

8 g. (2 moles) of sodium hydroxide in 50 ml of water was placed in RBF along with 5 g (0.266 mole) of gallic acid. The flask was immediately stoppered, and then reaction mixture was shaken occasionally until all the acid was dissolved; 6.7 ml (0.71 mol) of dimethyl sulfate was then added and the flask was stirred for 1hr, during this temperature was maintained below 30–35⁰C. The flask was then fitted with a reflux condenser and refluxed for 2 hr. The ester thus produced was saponified by addition of 2 g. of sodium hydroxide dissolved in 3 ml of water and refluxing for 2 hours. The reaction was monitored by TLC. The reaction mixture was then cooled and acidified

with dilute HCl, the precipitated 3,4,5-trimethoxybenzoic acid was filtered and washed with cold water. The product 3,4,5-trimethoxybenzoic acid (TMBA) was recrystallized from boiling water using decolorizing carbon (Scheme 3a). Formations of products were conformed by IR spectra which have shown absence of COOH stretch. The compounds were also confirmed by melting point (m.p.), thin layer chromatography (TLC), and gas chromatography-mass spectrometry (GC-MS).

Synthesis of Methyl 3, 4, 5 trimethoxy benzoate (4)

2gm (1mol) 3, 4, 5-trimethoxy benzoic acid was dissolved in 10 ml methanol and placed in RBF. To it 0.74gm (1.25 mol) dimethyl sulphate and 2.01gm (1.25 mol) anhydrous Sodium bicarbonate was added and the reaction mixture was refluxed for 8-10 hr. The reaction was monitored by TLC. The reaction mixture was then dumped in ice cold water and the precipitate was collected by suction and dried. The product Methyl 3, 4, 5 trimethoxy benzoate (MTMB) obtained was recrystallized from ethanol (Scheme 3b).



Scheme 2- (a) excess NaOH, DMS Reflux; (b) DMS, NaHCO₃

Evaluation of Antioxidant ability

DPPH scavenging activity (17)

DPPH (2.365 mg) was dissolved in 10 mL of 95% ethanol. Test substance was dissolved in 95% ethanol so as to contain 12 mg in 12 mL. The stock solutions were diluted with 95% ethanol to make solution containing 10-400 ppm of the substance under test. Percentage scavenging of DPPH radical was calculated.

Pharmacological Screening:

The effect of gallic acid derivatives was assessed using a single dose. The doses of derivatives were equivalent to the molecular weight of gallic acid.

Tacrine Induced Vacuous chewing movements in Rats (18)

Rats (150-200g) divided in nine groups; each group containing five animals received vehicle or the gallic acid derivatives intraperitoneally 30 min before tacrine (2.5 mg/kg i.p.) numbers of vacuous chewing jaw movements were counted for period of 60 min.

Haloperidol Induced Catalepsy in mice (19)

The mice (22-25 g) divided in nine groups, each group contain five animals, One of which treated with Haloperidol (1 mg/kg i.p.) considered as a control group. Other group received Gallic acid derivatives before administration of haloperidol (1mg/kg, i.p.). The duration of catalepsy was recorded from the time all animals were placed over the bar till the time they removed both forepaws from the bar or climbed over the bar. Duration of catalepsy was measured in seconds at 30, 60, 90, 120,150, and 180 min after haloperidol using the bar test. The cut of time was five min.

Results and Discussion

The esters of gallic acid were prepared according to the scheme 1A. Formations of esters were conformed by IR spectra which have shown absence of COOH stretch. The compounds were also confirmed by melting point (m.p.), thin layer chromatography (TLC), and gas chromatography-mass spectrometry (GC-MS).

Methyl gallate: m.p.186-188⁰C, Rf: 0.58, yield 78%, % C = 53.17; %H = 4.34, % O = 58.0%

GCMS: CH₃- m/e 184, 4.63%, [C₈H₈O₅]⁺; 69, 1.34%, [C₇H₅O₅]⁺;153, 100%, [C₇H₅O₄]⁺; 139, 1.33%, [C₇H₆O₃]⁺; 125, 24.98%, [C₆H₅O₃]⁺; C₂H₅- m p - [154-156⁰C, Rf 0.63, yield 70%], C 54.10%, H 5.05% O 40.85%, GC-MS, m/e 198, 3.63%, [C₉H₁₀O₅], 153, 100%, [C₇H₅O₄], 125, 30%, [C₆H₅O₃]; C₃H₇- m. p.150-152⁰C Rf 0.68 yield 70%, C 56.60%,H 5.66% O37.74%, GC-MS, m/e 212, 4.17%, [C₁₀H₁₂O₅]⁺, 195, 0.75%, [C₉H₇O₅]⁺, 183, 4.33%, [C₈H₇O₅]⁺, 170, 6.58%, [C₇H₆O₅]⁺, 153, [C₇H₅O₄]⁺, 125, [C₆H₅O₃]⁺.

Butyl gallate: m.p.132-134⁰C, Rf: 0.76, yield 67%), C - 56.4%, H - 6.19%, O - 37.4%, GC-MS,- m/e 226, 46.27%, [C₁₁H₁₄O₅]⁺(molecular ion peak), 209, 11, [C₉H₁₀O₅]⁺, 181, 4.79%, [C₈H₅O₅]⁺, 170, 100%, [C₇H₅O₅]⁺, 153, 80.36%, [C₇H₅O₄]⁺, 125, 19.62%, [C₆H₅O₃]⁺,

Phenyl gallate: m. p. 154-156⁰C, Rf = 0.65, yield – 70%, % C = 52.7.; % H = 5.05; % O = 42.25, GC-MS- m/e 240, 20.37%, [C₁₁H₁₂O₅]⁺, 266, 7.99%, [C₉H₉O₅]⁺, 209, 0.54%, [C₈H₇O₅]⁺, 183, 1.74%, [C₈H₇O₅]⁺,170, 100%, [C₇H₅O₅]⁺,153, 76.15%, [C₇H₅O₄]⁺,125, 16.26%, [C₆H₅O₃]⁺.

Synthesis of 3, 4, 5 Trimethoxybenzoic acid

3, 4, 5 Trimethoxybenzoic acid was synthesized by reaction of gallic acid with dimethyl sulphate in presence of NaOH. The yield was 60% with m.p.168⁰C, Rf: 0.86, C- 56.6%, H-10.0%, O- 43.4%.

IR spectra: C=O stretch (1684.85), C=C stretch (Aromatic) (1587.47), C-O-C symmetrical stretch (1226.47), C-O-C asymmetrical stretch (1226.77), OH stretch (2945.40)

GCMS: m/e 212, 100%, [C₁₀H₁₂O₅]⁺, 197, 58.77%, [C₉H₉O₅]⁺, 169, 13.08% [C₉H₁₁O₃]⁺, 154, 14.87%, [C₈H₈O₃]⁺

Synthesis of Methyl 3, 4, 5 trimethoxy benzoate

Methyl 3, 4, 5 trimethoxybenzoate was synthesized by reaction of 3,4,5 trimethoxy benzoic acid with dimethyl sulphate and sodium bicarbonate It was confirmed by IR spectra which have shown absence of phenolic OH stretch at 3290 cm⁻¹ and absence of COOH stretch, m.p., TLC, elemental analysis, GC-MS. The yield of methyl 3,4,5, trimethoxybenzoate was 55% with m.p. 82⁰C, Rf: 0.96, C 56.4%,H 6.19%,O37.4%.

GCMS: m/e 226, 100%, [C₁₁H₁₄O₅]⁺, 211, 52.87%, [C₁₀H₁₁O₅]⁺, 195, 23.57%, [C₁₀H₁₁O₄]⁺,155, 24.67%, [C₇H₂O₄]⁺

IR data: C=O stretch (1714.77), C=C stretch (1591.33), C-O-C symmetrical stretch (1132.36), C-O-C asymmetrical stretch (1228.70), C-H stretch Ar (2953)

Preparation of 3, 4, 5 Tri acetoxybenzoic Acid

Results yield 75%, m.p.166⁰C, Rf: 0.78. IR spectra: C=O stretch (1714.77), C=O stretch in ester (1772.64), C-H stretch (Ar 2820.02), OH stretch (2991.69).

DPPH scavenging activity of various gallic acid derivatives

Table 1 shows the scavenging efficiency of gallic acid derivatives on DPPH in ethanol. Comparing the DPPH scavenging activity of gallic acid derivatives and trimethoxy-, triacetoxy-, and methyltrimethoxy benzoic acid, the order for DPPH scavenging efficiency in ethanol was GA > MG > PG > PhG > BG > TMBA > TABA > MTMB.

This indicated that optimum chain length for gallic acid esters to act as powerful antioxidant is four carbon atoms in the aliphatic chain. The antioxidants commonly used in practice have free –OH groups. Thus free hydroxyl group on phenyl ring is necessary for radical scavenging activity of compound in this series. When these hydroxyl groups are converted to trimethoxy or triacetoxy group, the DPPH scavenging ability is drastically reduced. This observation is in line with that of Savi et al., (15). Eventhough GA, MG, PG, PEG, BG, PTB, IPTB, have the same number and distribution of hydroxyl groups in their molecules, their scavenging efficiency on DPPH varies, this suggests that the steric effect also play an important role in free radical scavenging activity.

Since antioxidants have been tested for Antiparkinson's activity, we were interested in determining the antiparkinsonian activity of these compounds. Table 2 shows effect of gallic acid derivatives on tacrine induced VCM's in rats. The order of reduction in VCM was MG > PG > TABA > GA > BG > PhG > TMBA > MTMB. The effect of TMBA and MTMB could not reach the level of significance. The 3,4,5, triacetoxy benzoic acid in which hydroxyl group was esterified with acetyl, even though did not possess antioxidant ability in-vitro, possessed the Antiparkinson activity comparable to gallic acid in vivo. It may be due to the metabolism (hydrolysis) of TABA to gallic acid. Thus MG, PG, BG which have slightly more hydrophobicity than gallic acid resulted in more activity than the parent compound in-vivo. Hence it can be stated that neuroprotective effect of compounds in this series against oxidative stress damage not only depends on its capacity to scavenge free radicals, but also depends on its hydrophobic properties that allow it to reach 'reaction site'. Among the derivatives of trimethoxy benzoic acid it was found that TMBA and MTMB significantly reduced VCM although these compounds were lacking in antioxidant ability.

Table 3 shows effect of gallic acid derivatives and trimethoxy benzoic acid derivatives on haloperidol induced catalepsy in mice. Drugs that increase dopaminergic activity or inhibit cholinergic activity inhibit neuroleptic-induced catalepsy (19). It has been proposed that reactive oxygen species play a causative role in neurotoxic effects induced by haloperidol (20). Haloperidol caused more oxidative stress along with a significant reduction of important antioxidant parameters (21, 22). Naidu et al., (23) have shown that antioxidants inhibit haloperidol induced catalepsy. The order of activity in haloperidol induced catalepsy model in mice was: TMBA > MTMB > TABA > PG > BG > MG > PhG > GA. From this result it was noted that trimethoxy benzoic acid and its derivatives did not possess antioxidant ability but these compounds were found to inhibit haloperidol-induced catalepsy. The potency order of gallic acid derivatives in haloperidol-induced catalepsy differs from that observed in the tacrine induced VCMs. Shivakumar and Ravindranath (24) have shown that haloperidol induces oxidative stress whereas Saxena et al., (25) have shown that tacrine suppresses oxidative stress. Stress is known to modify haloperidol-induced catalepsy. Yntema and Korf, (26) and Dijk et al., (27) have reported inhibition of haloperidol-induced catalepsy by stress. It is reported earlier that antioxidant activity may or may not be mediated via dopamine D2 receptors (9, 10). Therefore the potency order of gallic acid derivatives in tacrine-induced VCMs does not match with their ability to inhibit haloperidol-induced catalepsy. Thus it is concluded that gallic acid derivatives possess antioxidant activity and antiparkinson activity and lack of correlation between the antioxidant ability and antiparkinson activity may be ascribed to steric- steric effect, involvement of dopamine D2 receptor in the antioxidant activity, and oxidative stress.

Table 1- DPPH scavenging activity of gallic acid derivatives

Sr.No	Name of compound	Free Hydroxy group(s)	IC 50 value (Conc. In ppm)
1	GA	3	6.0 ± 0.1
2	MG	3	7.2 ± 0.1
3	PG	3	8.2 ± 0.1
4	BG	3	12.2 ± 0.2
5	PhG	3	9.3 ± 0.3
6	MTMB	-	nil
7	TMBA	-	78.0 ± 1.1
8	TABA	-	198.2 ± 2.1

Table 2: Effect of various synthetic derivatives of Gallic acid on tacrine-induced Vacuous chewing movements in rats

Sr. No	Treatment group (mg/kg)	VCM (Mean ± SEM)	No. of burst (Mean ± SEM)
1	Vehicle	1297.0 ± 53.52	221.2 ± 22.55
2	GA (150)	370.2 ± 22.16*	140.4 ± 12.71 *
3	PG (187)	240.0 ± 14.33*	91.2 ± 8.92*
4	MG (162)	194.8 ± 12.69*	82.4 ± 8.57*
5	BG (199)	345.2 ± 60.58*	108.2 ± 24.04*
6	PhG (217)	571.6 ± 34.05*	177.6 ± 4.19
7	TABA (261)	246.5 ± 24.83*	98.8 ± 10.68*
8	MTMB(199)	840.8 ± 35.96	221.8 ± 19.5
9	TMBA(187)	660.2 ± 35.35	186.0 ± 9.52
	F _{8,36}	97.68	13.88
	P	0.000	0.000

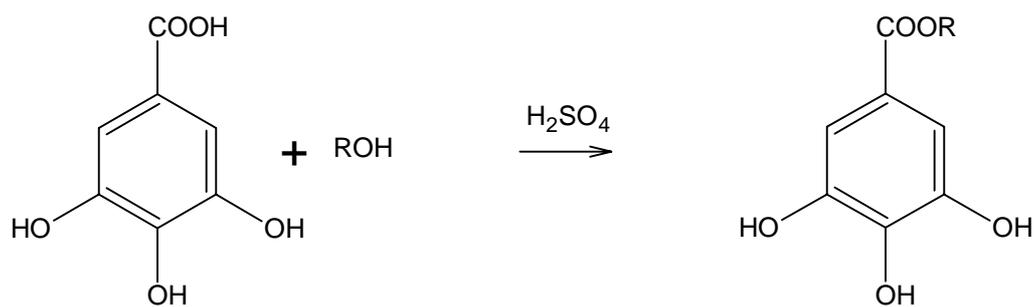
n = 5, * P < 0.005 compared with vehicle treated group.

Table 3: Effect of various synthetic derivatives of gallic acid on haloperidol-induced catalepsy in mice

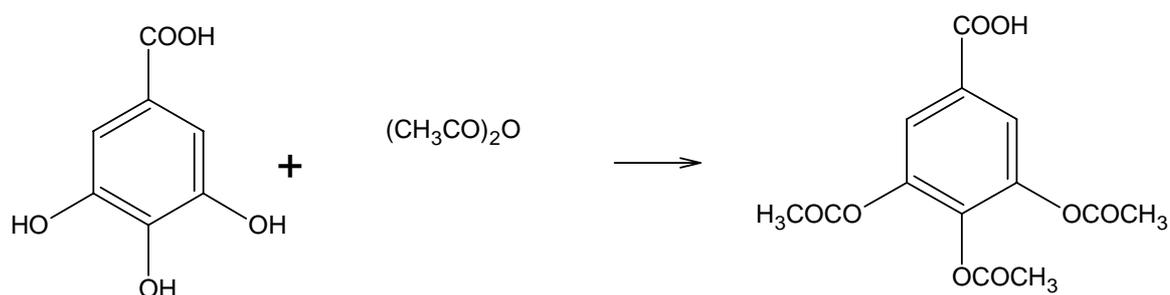
Sr. no	Treatment groups (mg/kg)	30 min	60 min	90 min	120min	150min	180 min
1	Vehicle	104.0 ± 22.53	138 ± 30.5	254.4 ± 36.15	252.0 ± 4.8	267.0 ± 33.0	220.8 ± 31.52
2	GA (150)	57.67 ± 8.45*	248.0 ± 49.5	203.7 ± 50.5	267.0 ± 33.0	225.7 ± 42.72	115.3 ± 3.18*
3	MG (162)	115.0 ± 33.78	108.7 ± 11.9	167.3 ± 6.0	189.0 ± 9.0*	267.0 ± 33.0	109.7 ± 16.76*
4	PG (187)	86.67 ± 51.67	69.33 ± 36.9	72.33 ± 25.2*	132.7 ± 14.85*	68.67 ± 17.75*	69.33 ± 7.96*
5	BG (199)	209 ± 54.35	231.0 ± 35.8	236.7 ± 66.33	138.7 ± 14.5*	153.78 ± 51.77	257.3 ± 34.90
6	PhG (217)	196.7 ± 65.6	64.3 ± 27.8	104.0 ± 24.6*	69.0 ± 24.60*	91.67 ± 17.4*	152.0 ± 25.17*
7	MTMB (199)	12.67 ± 2.02	42.0 ± 15.4	15.67 ± 4.17*	31.33 ± 17.85*	28.33 ± 13.35*	18.0 ± 4.93*
8	TMBA (187)	17.33 ± 2.02	13.67 ± 8.21*	10.33 ± 2.33*	27.33 ± 10.09*	30.67 ± 5.36*	27.0 ± 8.88*
9	TABA (261)	27.33 ± 10.59	8.67 ± 5.23*	27.67 ± 5.36*	28.33 ± 7.17*	32.33 ± 3.71*	43.67 ± 4.31*
	F _(8,18)	4.07	9.58	8.74	29.75	12.30	19.35
	P	0.006	0.000	0.000	0.000	0.000	0.000s

n = 5, * P < 0.005 compared with haloperidol treated group. One-way ANOVA followed by Dunnett's test

Scheme I



Scheme II



Scheme III

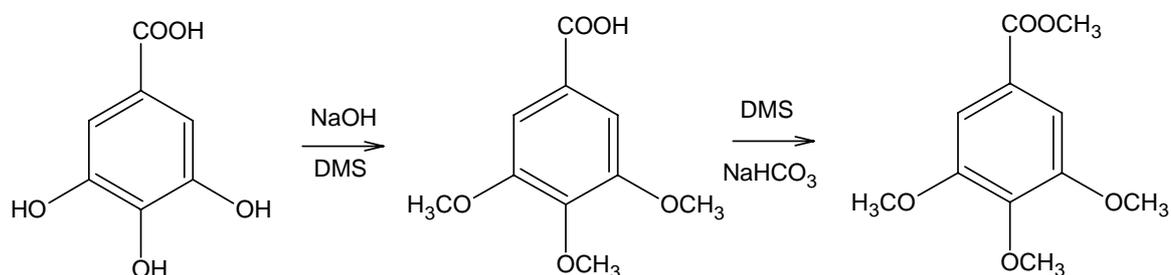


Fig 1: Schemes used to synthesize gallic acid derivatives

Acknowledgements

The authors acknowledge Prof. V. M. Aurangabadkar, Principal, MGV Pharmacy College, Nashik for providing facilities.

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