A Comprehensive Review on the Synthesis of Mangiferin Derivatives and their Multiple Biological Activities

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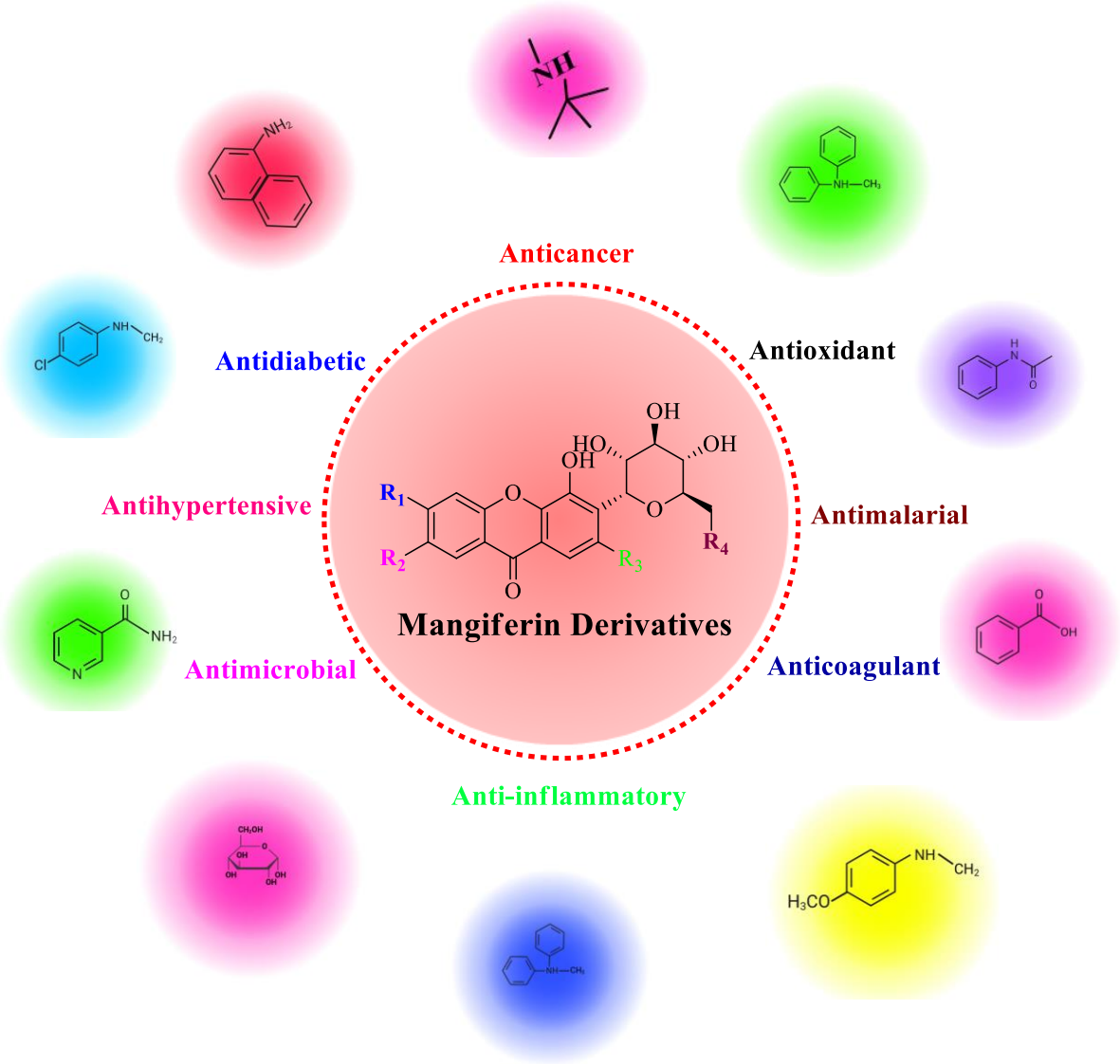
Abstract: Mangiferin always draws the attention of traditional as well as modern medicinal chemists because of its ease of chemical derivatization and diverse biological activities, including anticancer, anti-inflammatory, neuroprotective, antidiabetic, analgesic, antimalarial, anticonvulsant, laxative, cardiotonic, hemopoietic, antioxidant, antimicrobial, antipsychotic, anticoagulant, and antihypertensive properties. This review focuses on a detailed and updated overview of the synthesis of mangiferin derivatives and their diverse biological activities, with examples from both patented and non-patented literature.

Graphical Abstract:



1. Introduction

Mangiferin, a naturally occurring polyphenolic heterocyclic organic compound, also known as quinomine or alpizarin, that is generally found in plants such as Mangifera indica, which belongs to the class of Xanthones[1-3]. 1,3,6,7-tetrahydroxy-2-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)-9H-xanthen-9-one, or mangiferin, has two of the important functionalized rings, xanthone and pyranose[4]. Broad research discovers its chemical and pharmaceutical properties, basically introducing structural modifications to its effectiveness with respect to various biological activities like anti-inflammatory, anticancer, neuroprotective, immunosuppressive anti-tumour, antidiabetic, laxative, antiviral, cardiotonic, hemoptysis, analgesic, cytoprotective effect, antimalarial, antioxidant, antimicrobial, antipsychotic, antihypertensive activities etc[5-56]. Mangiferin has also exhibited good inhibitory activities on kinase family enzymes[21-27, 50, 57-61]. Mangiferin has gained great importance owing to its anticancer activity in lung cancer, colorectal cancer, and breast cancer[62-72]. Various drug candidates are available pharmaceutically; containing xanthone and the pyranose ring as a pharmacophoric moiety, and are also available in clinical development to reveal the utility of mangiferin as a pharmacophoric molecule[73]. This review provides a comprehensive, detailed, and updated overview of mangiferin about chemistry and their diverse biological activities, covering patented and non-patented literature.

2. General Synthetic Strategies of Mangiferin and its derivatives

The significant research work of researchers has developed of various synthetic methodologies to synthesize numerous potential derivatives of mangiferin to manage and treat various diseases[46, 74, 75]. Some of which are defined in the schemes below:

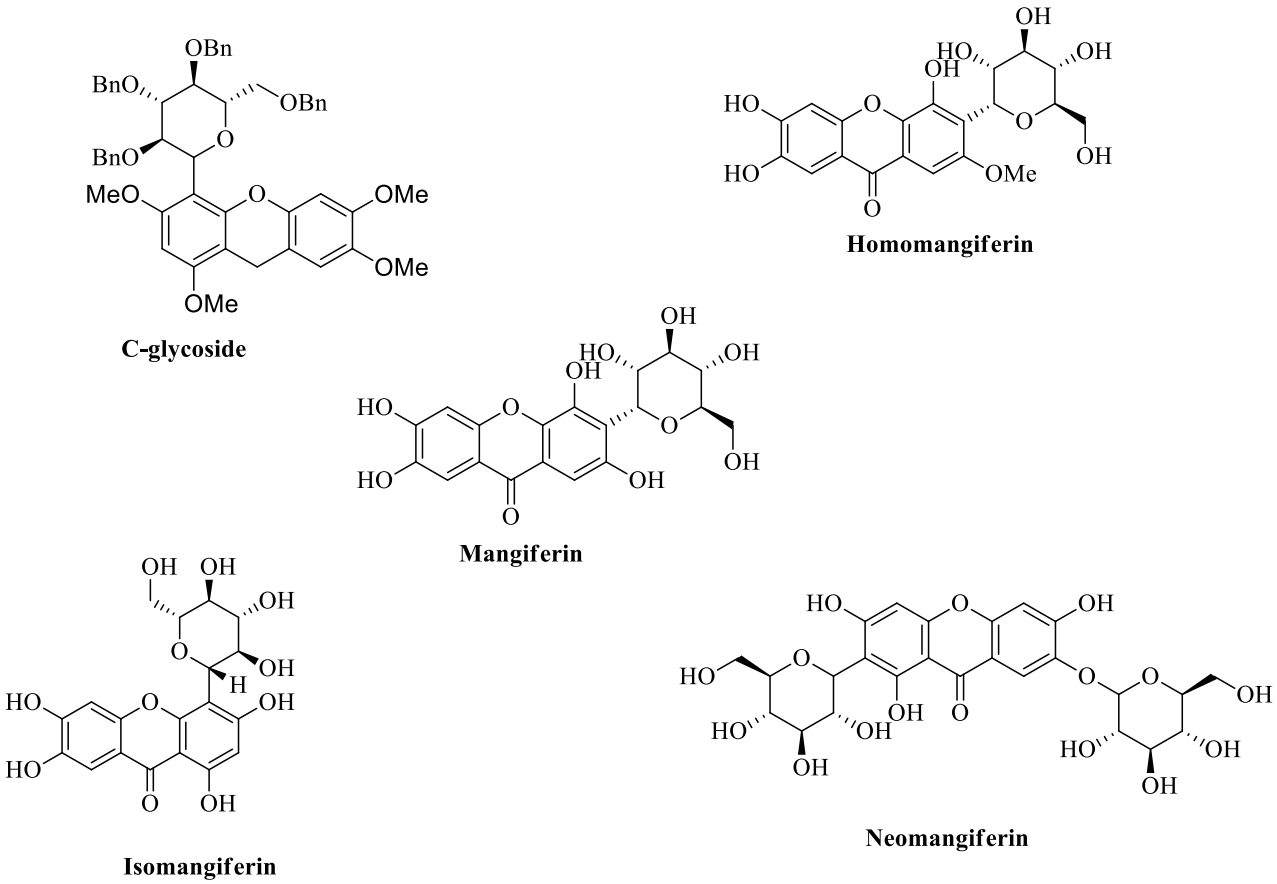


Figure 1. Structure of Mangiferin and its isoforms[76-89]

2.1. Mangiferin analogues as PTP1B inhibitors

In 2007, Wang Hu, Hg., Wang, Mj., Zhao, Qj. *et al.*[90] reported the synthesis series of mangiferin derivatives **1-9** (Fig 2) as depicted in scheme 1.

Synthesis of reported compounds **1-9** begins with the reaction of mangiferin solution in dry dimethylformamide that was reacted with RX (alkyl halide) and K_2CO_3 with continuous stirring at 60 °C for 10 hours. The reaction mixture gave a residue that was further purified by column chromatography using dichloromethane (CH_2CL_2) and Methanol (CH_3OH) as eluent to give desired compounds **1-9.**

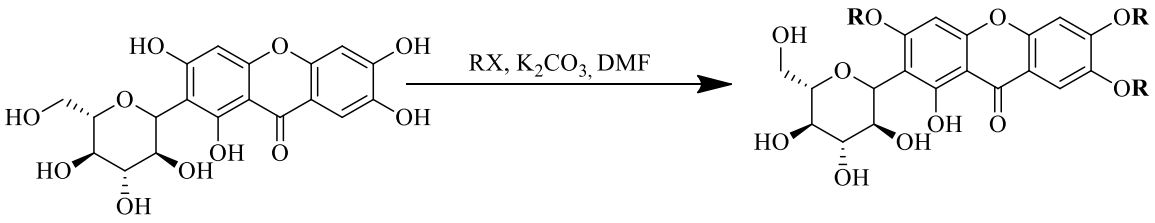
2.1.1. Biological activity

Mangiferin show effective inhibitory activity at 50 µM concentration that has been shown antidiabetic action by inhibiting Protein tyrosine phosphatase 1B (PTP1B) in table 1. Compound **6** and **9** shown 100% and 62.5% inhibition against PTP1B.

Table 1. In vitro PTP1B Enzyme Inhibitory Activity of the Compounds

Compounds	**Ratio of inhibition, Percentage**	
	500 µM	**50 µM**
1	24.07	-
2	24.97	-
3	22.02	-
4	19.60	-
5	47.70	-
6	5.41	100.0
7	*	10.68
8	51.14	26.14
9	*	62.50

***Mean deposition were found whereas buffer was added to the test sample solution.*



(50-65% yield)

Scheme 1. Synthesis of Mangiferin derivatives 1-9[90]

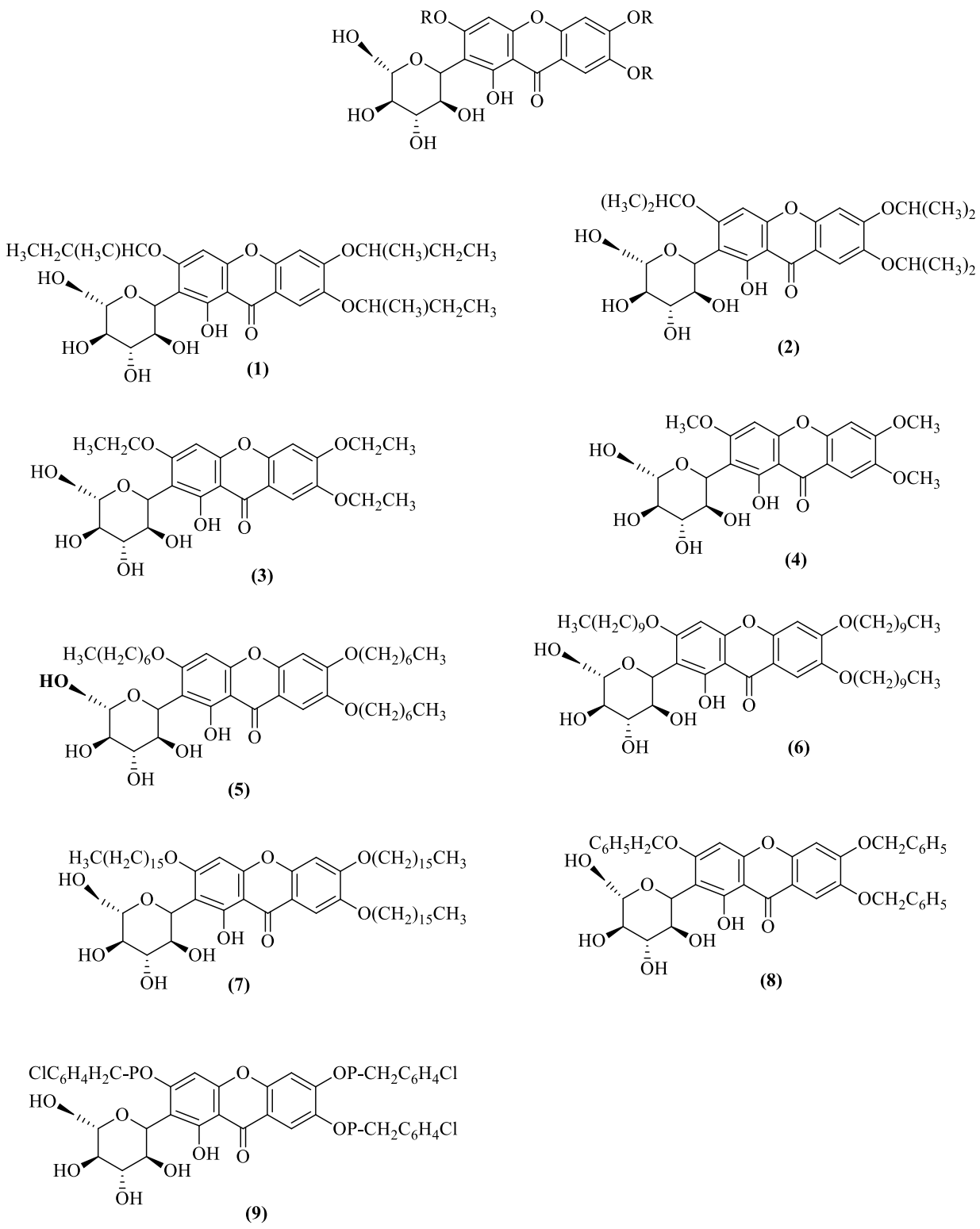
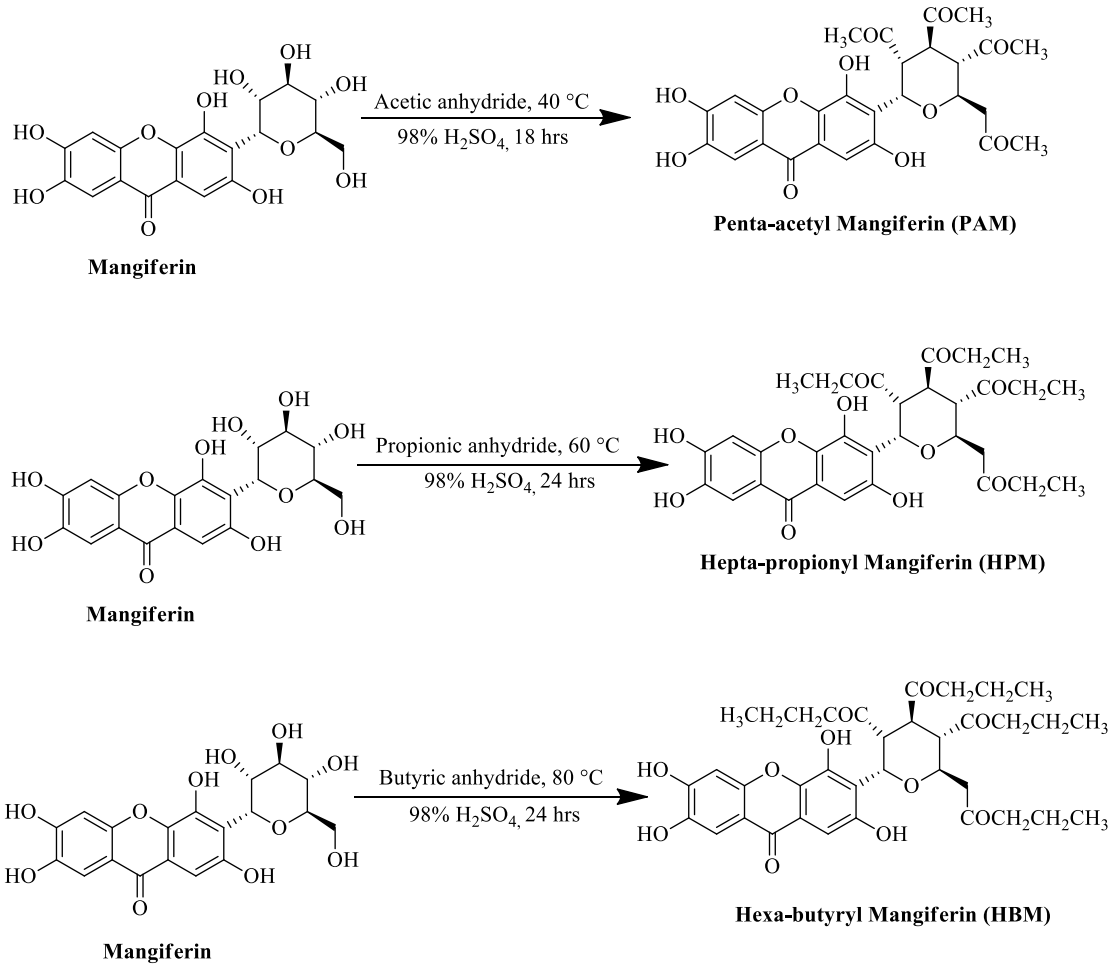


Figure 2. Mangiferin derivatives as PTP1B inhibitors[90]

2.2. Mangiferin analogues as antidiabetic agents

In 2013, Deng Jia-Gang *et al*.[91] synthesized novel three esterified-derivatives of mangiferin (PAM, HPM and HBM), as represented in scheme 2.



Scheme 2. Synthesis of Esterified Mangiferin Derivatives[91]

Synthesis of **PAM** using mangiferin in the mixture of solution of acetic anhydride, and 98% H_2SO_4 with continuous stirring at 40 °C for 18 h in a water bath. The reaction mixture further processed by washing and extracted then purified by column chromatography using chloroform : ethyl acetate : acetone (7 : 2 : 1) as eluent to give desired compounds **PAM.**

Synthesis of **HPM** using mangiferin in the mixture of solution of propionic anhydride, and 98% H_2SO_4 with continuous stirring at 60 °C for 24 h in a water bath. The reaction mixture further processed by washing and extracted then purified by column chromatography using chloroform : methanol (25 : 1) as eluent to give desired compounds **HPM.**

Synthesis of **HBM** using mangiferin in the mixture of solution of butyric anhydride, and 98% H_2SO_4 with continuous stirring at 80 °C for 24 h in a water bath. The reaction mixture further processed by washing and extracted then purified by column chromatography using petroleum ether : chloroform : acetone (10 : 7 : 3) as eluent to give desired compounds **HBM.**

2.2.1. Biological activity

Esterified analogues of mangiferin showed good antidiabetic activity. The antidiabetic activity of the esterified analogues of mangiferin was assessed in a streptozotocin-induced hyperglycemia mouse model. Table 2 shows that the positive control (metformin), PAM (0.5, 0.25 millimole/kg^{-1}), HPM (0.5, 0.25 millimole/kg^{-1}), and HBM (0.5, 0.25, 0.125 millimole/kg^{-1}) showed good anti-diabetic activity ($P < 0.01$). The mangiferin (1, 0.5 millimole/kg^{-1}), PAM (0.125 millimole/kg^{-1}), and HPM (0.125 millimole/kg^{-1}) showed least hypoglycemic activity ($P < 0.05$); the mangiferin (0.25 millimole/kg^{-1}) had the potential for a anti-diabetic effect. The findings showed that the hypoglycemic activity of all mangiferin esterified analogues is greater than that of mangiferin in vivo studies.

Table 2. Comparative in vitro studies for antidiabetic activity of mangiferin and its derivatives with standards

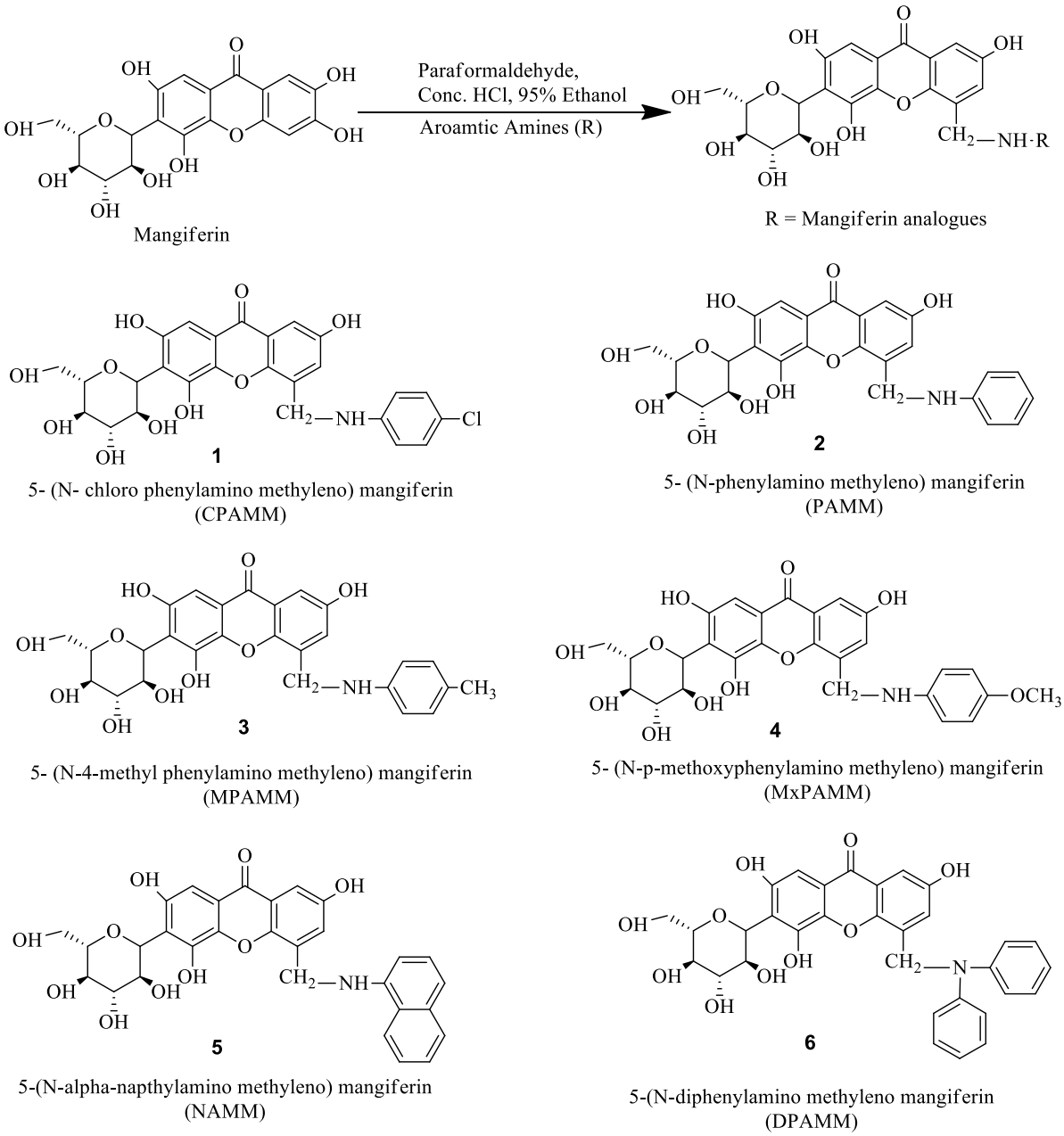
Sr. No.	Groups	Dose (millimole/kg^{-1})	c1(mmol/L−1)	c14 (mmol/L^{-1})	R/%
1.	Normal control	-	7.51 ± 0.59	7.12 ± 0.77	4.96 ± 10.21
2.	Hyper-glycemic model	-	17.727 ± 5.245	16.61 ± 5.18	3.514 ± 25.34
3.	Positive control (Metformin)	-	17.738 ± 5.735	7.50 ± 1.45	54.21 ± 14.36**
4.	Mangiferin	1.0	16.56 ± 5.06	11.06 ± 3.92	28.27 ± 26.99*
		0.5	17.64 ± 5.07	12.69 ± 5.02	27.38 ± 18.09*
		0.25	17.21 ± 5.27	13.68 ± 4.98	19.48 ± 17.34
5.	PAM	**0.5**	18.22 ± 6.09	10.19 ± 4.85	41.92 ± 22.23**
		0.25	17.60 ± 5.41	10.58 ± 3.39	35.78 ± 24.18**
		0.125	17.1 ± 5.38	11.81 ± 4.78	28.26 ± 24.72*
6.	HPM	**0.5**	17.60 ± 5.88	10.54 ± 2.74	35.21 ± 18.53*
		0.25	18.31 ± 5.71	11.94 ± 6.16	35.44 ± 20.96**
		0.125	18.27 ± 6.28	12.25 ± 6.93	30.83 ± 21.74*
7.	HBM	**0.5**	18.03 ± 4.67	11.24 ± 3.53	37.16 ± 15.96**
		0.25	18.52 ± 6.26	10.98 ± 2.86	35.03 ± 20.64**
		0.125	16.93 ± 5.04	11.24 ± 3.65	34.21 ± 18.30**

Note: **P<0.05, **P<0.01, t-test compared to the hyperglycemic model group.*

2.3. Mangiferin analogues as antimicrobials

In 2012, Saurabh K. Sinha *et al.*[92] synthesized a series of novel mangiferin analogues **1-6**, as depicted in Scheme 3. Generally, to synthesize mangiferin analogues an equivalent molar solution of mangiferin, concentrated hydrochloric acid, paraformaldehyde, 95% ethanol, and aromatic amines are used, the reaction

mixture was refluxed at 80 °C for 2 hours, and then the reaction mixture was cooled to room temperature and kept in the refrigerator overnight. The resulting reaction mixture was diluted, washed with water, filtered, and crystals were recrystallized from ethanol.



Scheme 3. Synthesis of mangiferin analogues[92]

2.3.1. Biological activity

The antibacterial and antifungal activity of solutions containing varying amounts of mangiferin and its novel analogues.

Table 3. Biological activity of mangiferin and its analogues as antimicrobial and antifungal.

Sr. No.	Compounds	Conc. %	Antibacterial activity Inhibition				Antifungal activity Inhibition	
			Bac. pumilus	***Bac. cereus***	***Sal. virchow***	***Pse. aeruginosa***	***Asp. flavus***	***Ther. aurantiacus***
1.	Mangiferin	15	18	15	22	0	0	0
		20	20	17	26	0	0	0
		25	23	18	29	0	0	0
		30	nt*	nt*	nt*	0	12	18
2.	PAMM	15	16	12	19	0	0	0
		20	19	15	22	0	0	0
		25	22	16	23	0	0	0
		30	nt*	nt*	nt*	10	11	14
3.	CPAMM	15	15	12	20	0	0	0
		20	17	14	21	0	0	0
		25	18	15	23	0	0	0
		30	nt*	nt*	nt*	8	11	13
4.	MPAMM	15	17	15	20	0	0	0
		20	19	17	22	0	0	0
		25	22	19	25	0	0	0
		30	nt*	nt*	nt*	10	14	15
5.	MxPAMM	15	18	14	20	0	0	0
		20	19	17	21	0	0	0
		25	22	19	23	0	0	0
		30	nt*	nt*	nt*	9	11	16
6.	DPAMM	15	17	14	19	0	0	0
		20	18	15	20	0	0	0
		25	20	18	22	0	0	0
		30	nt*	nt*	nt*	9	12	14
7.	NAMM	15	18	13	18	0	0	0
		20	19	15	20	0	0	0
		25	21	18	23	0	0	0
		30	nt*	nt*	nt*	10	11	15

nt* = not tested against microorganisms

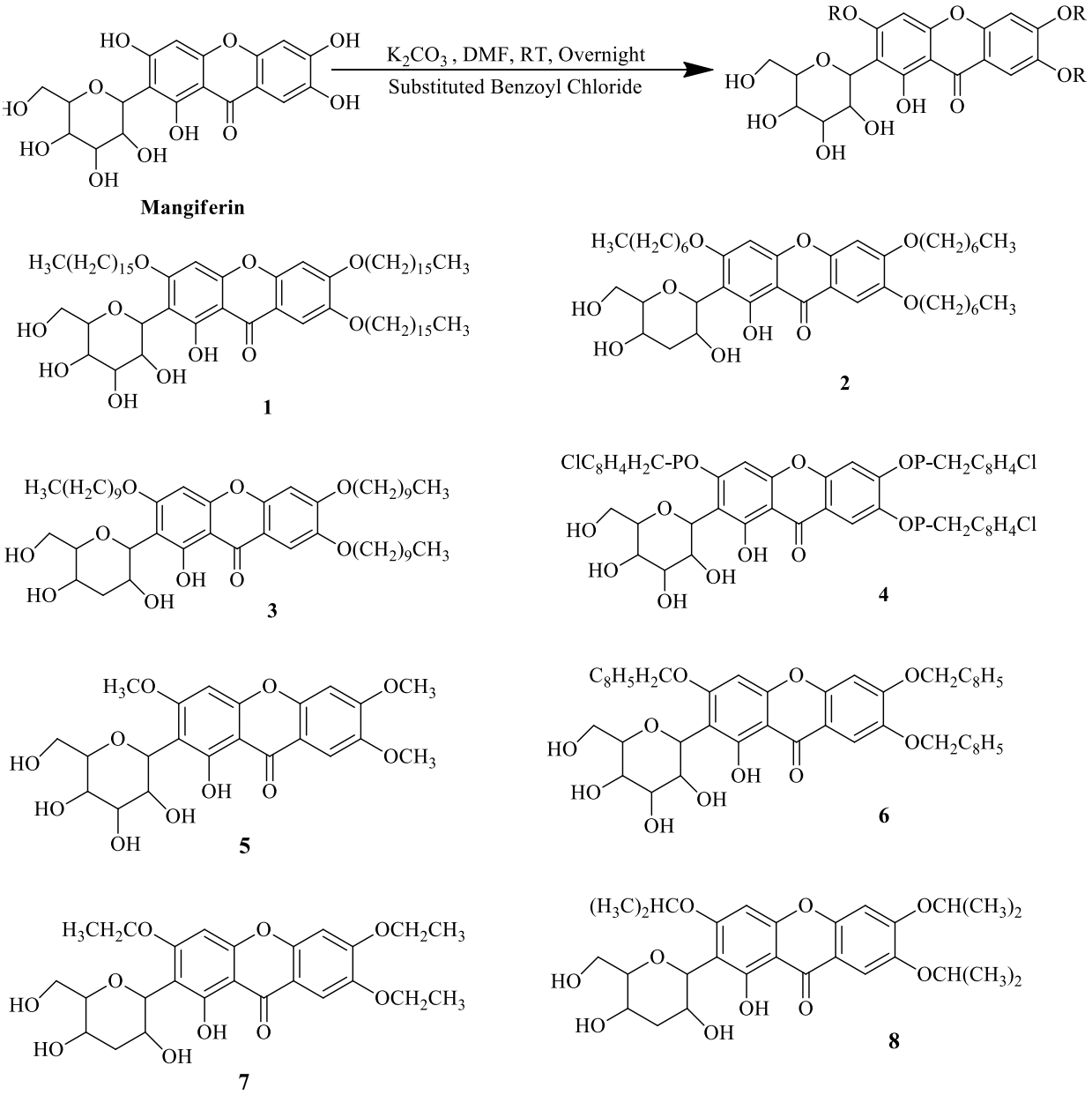
All of the examined bacterial and fungal stains showed increased activity at increasing concentrations, according to the data reported in Table 3. For all mangiferin analogues, the maximum inhibition against P. aeruginosa was detected at 30%, while the maximum inhibition for bacterial stains, namely B. pumilus, B. cereus, and S. virchow, was observed at a concentration of 25%. When T. aurantiacus and A. flavus fungal stains were investigated, it was shown that a 30% concentration of mangiferin analogues had good activity.

2.4. Mangiferin analogues as analgesics

In 2016, Karuna Shanker *et al.*[93] reported the synthesis of novel mangiferin derivatives **1-8** depicted in scheme 4. having analgesic action. To synthesized derivatives, in the solution of mangiferin, dry DMF, aryl/alkyl halide and K_2CO_3 were added at room temperature, kept for overnight with continuous stirring to get desired compound.

2.4.1. Biological activity

Mangiferin and its derivatives was found to be very effective analgesic and anti-inflammatory agents by inhibiting cyclooxygenase enzyme. Anti-inflammatory activity is measured in terms of inhibition phosphorylation of the NF-jB and JAK1–STAT1/3 pathways in gingival epithelia.



Scheme 4. Synthetic route and Synthesis of mangiferin derivatives as analgesic agents[93]

2.5. Mangiferin analogues as antioxidants and analgesic agents

In 2005, Ahsana DAR *et al.*[94] reported the synthesis of novel mangiferin derivatives **1-4** as antioxidants and analgesics, as depicted in Scheme 5. In an effort to enhance the antioxidant and analgesic effects, mangiferin's analgesic derivatives

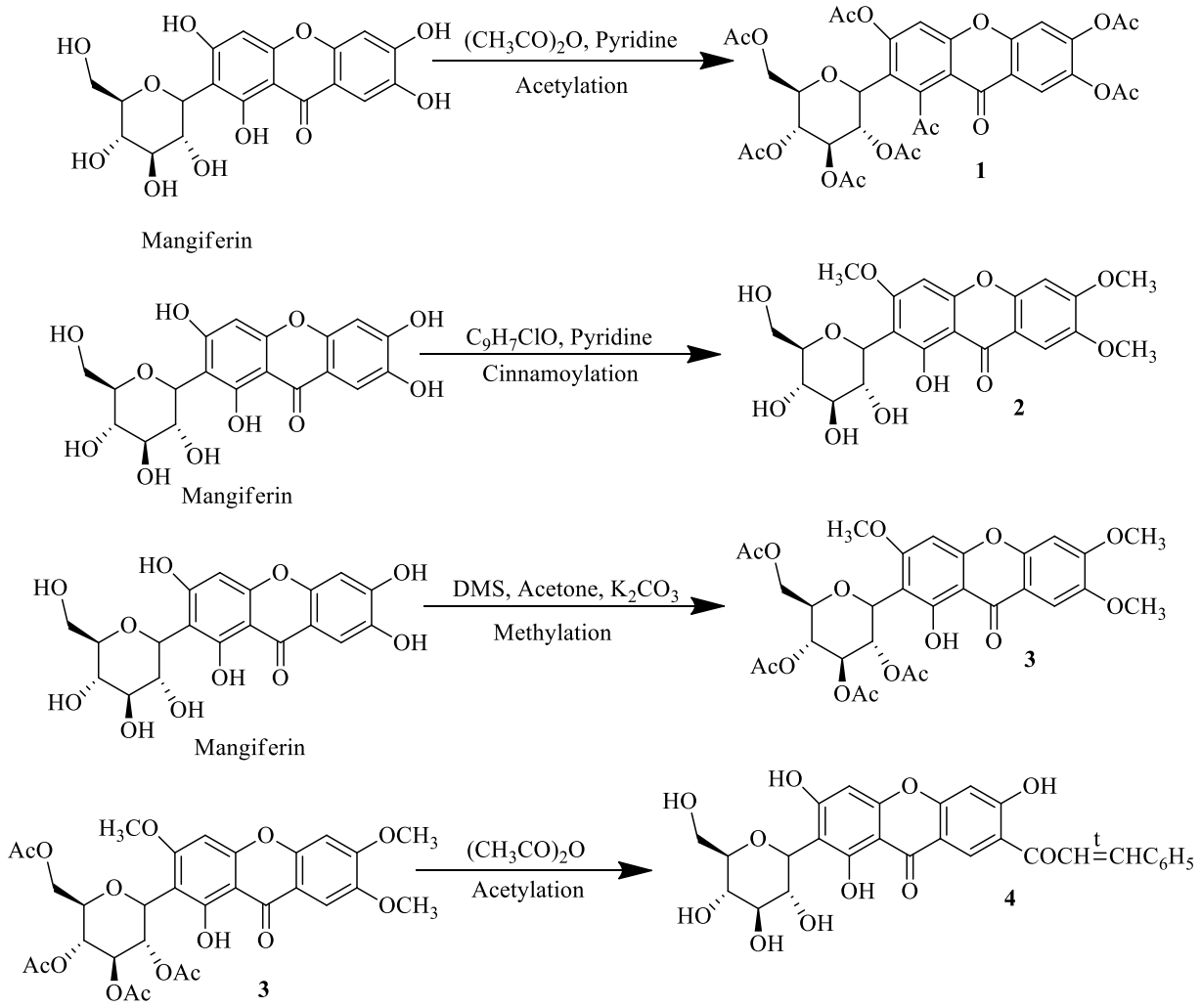
were synthesized through a noncatalytic reaction including acetylation, alkylation, benzylation, cinnamoylation, and methylation.

Using the acetylation of mangiferin, the solution of mangiferin is mixed with pyridine and reacts with acetic anhydride at room temperature for 36 hours. Further the reaction mixture is kept for evaporation, which gives compound **1** as residue that is subjected to purification to get desired compound **1**.

With the help of cinnamoylation of mangiferin in the solution of cinnamoyl chloride (C_9H_7ClO), mangiferin was reacted in the presence of pyridine at room temperature for 20 hours with continuous stirring. The resulting reaction mixture was kept for evaporation, which gave a residue that was fractionized with the solvent-solvent separation technique using the ratio of solvents, chloroform:methanol (9:1). The residue was washed with water and extracted with ethyl acetate. The combined organic layer was collected and concentrated to get the desired compound **2**.

Mangiferin was subjected to methylation, a solution of mangiferin in acetone was reacted with dimethyl sulfate (DMS) and K_2CO_3 with continuous stirring at room temperature for one week. The resulting reaction mixture was kept for evaporation, which gave a residue that was fractionized with the solvent-solvent separation technique using the ratio of solvents, chloroform:methanol (8:2). The combined residue was collected and concentrated to result in desired compound **3**.

Acetylation of Compound **3**: compound **3** carried out with acetic anhydride at room temperature for 7 hours. The resulting reaction mixture was kept for evaporation, which provides desired compound **4** as residue.



Scheme 5. Synthetic route and Synthesis of mangiferin derivatives as antioxidant and analgesic agents[94]

2.5.1. Biological activity

According to reported studies, mangiferin and its derivatives and B. ceiba leaf extract had analgesic and antioxidant properties in the different models that were examined. Using various tests, including DPPH, deoxyribose damage, and lipid peroxidation, the antioxidant efficacy of the extract and mangiferin was assessed. Using the DPPH assay, the leaves extract (BCL) of B. ceiba showed promising antioxidant activities. When it was divided into BCM and mangiferin, activity was

observed in mangiferin 1 and 3, which were derivatives with lower activity. It was found that 2 and 4 are not operational. The corresponding potency order appears to be rutin>}1>{3>{2>{ascorbic acid~>BCL>BCM based on antioxidant IC 50 values.

Table 4. Analgesic and antioxidant activity of mangiferin and its derivatives

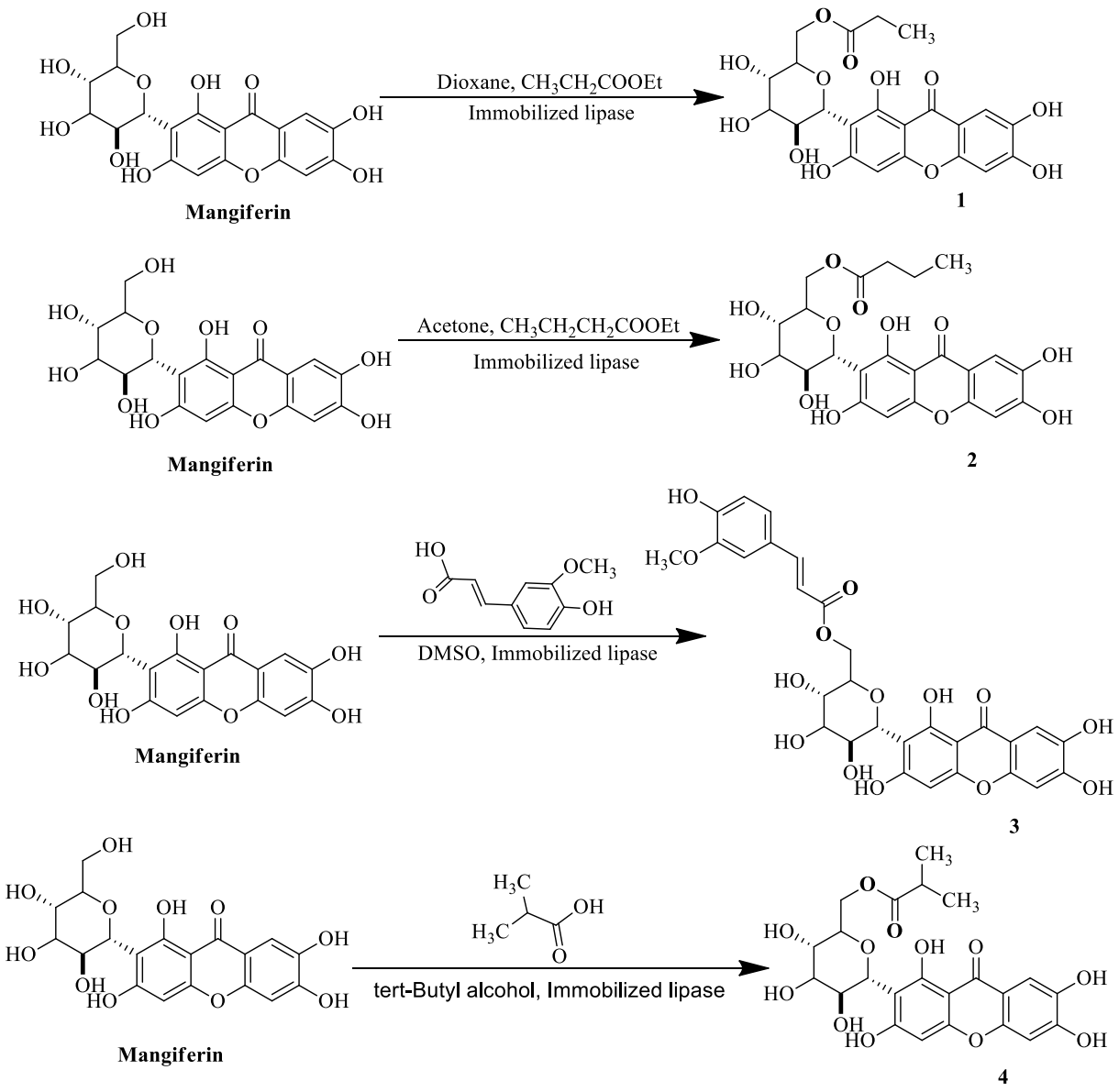
Sr. No	Dose (*m* g/ml)	BCL	BCM	Mangiferin	BCP-AC (1)	BCPC-1E (3)	Rutin	Ascorbic acid
1.	2	nt	nt	23.92±2.15	nt	nt	22.66±4.7	nt
2.	5	nt	nt	44.47±6.24	16.89±1.19	21.96±4.6	46.11±4.4	17.30±1.37
3.	10	31.06±4.4	14.82±0.6	77.24±7.21	35.85±1.55	40.96±6.8	85.07±2.0	39.45±3.88
4.	15	40.50±4.1	nt	83.75±3.6	61.16±3.73	nt	nt	48.50±1.24
5.	20	49.84±4.3	22.48±1.2	92.79±0.56	80.61±1.51	71.37±9.5	86.00±1.2	57.62±1.90
6.	30	68.35±5.45	35.19±1.9	93.56±0.05	92.43±0.17	78.36±11.	nt	nt
7.	50	93.09±1.7	51.73±5.4	nt	92.80±0.53	89.25±0.0	89.77±1.6	65.56±1.80
8.	IC_{50}	20.12±2.1	52.00±2.4	5.80±0.96	14.20±1.001	13.50±1.7	5.56±0.3	15.75±1.43

nt = not tested against microorganisms, BCL =Methanolic extract of B. ceiba leaves and BCM = Methanolic fraction of BCL

2.6. Synthesis of sugar esters based mangiferin derivatives

In 2010, Gang, D. J. *et. al.*[95] synthesized sugar ester-based mangiferin derivatives **1-4** with the help of the immobilized lipase that is illustrated in Scheme 6.

In an effort to synthesize sugar esters-based mangiferin derivatives, in the solution of ram mangiferin with dioxane, ethyl propionate, and in the presence of the immobilized lipase enzyme in a water bath at 60 °C for 24 hours, the reaction mixture was further concentrated with the help of a rotary evaporator that provided a residue that was subjected to purification with column chromatography using chloroform : methanol as eluent to provide the desired compound **1**.



Scheme 6. Synthetic route and its sugar ester derivative of mangiferin[95]

Synthesis of second sugar ester-based derivative of mangiferin, using raw mangiferin mixed with acetone and Propionic acid in the presence of immobilized lipase lipozyme in a water bath with thermostat control table at 60 °C for 24 hours, the reaction mixture was further concentrated with the help of a rotary evaporator that provided a residue that was subjected to purification with column

chromatography using chloroform : methanol as eluent to provide the desired compound **2.**

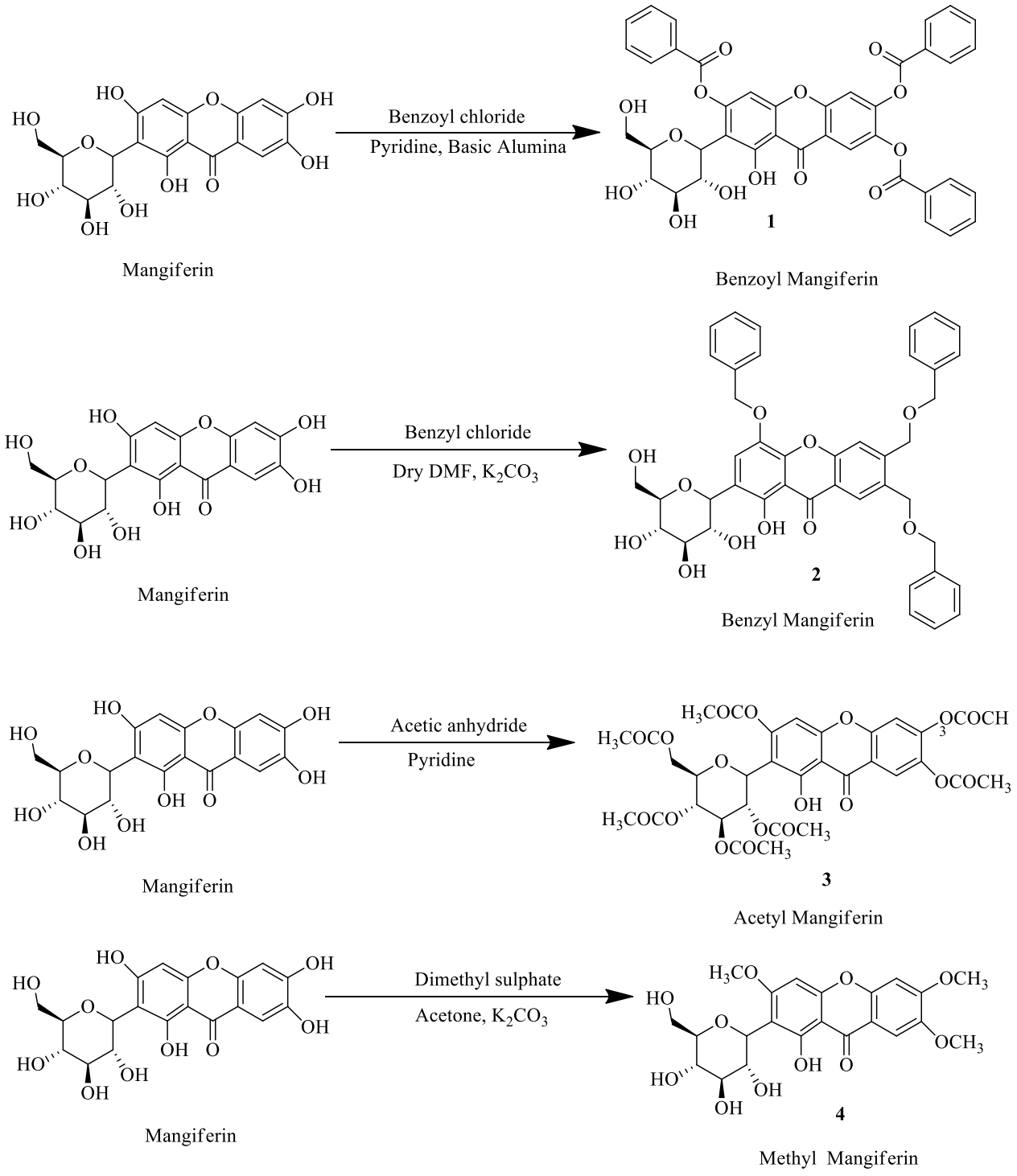
Synthesis of third derivative of sugar ester-based mangiferin, using raw mangiferin with isobutyric acid and tert-Butyl alcohol in the presence of immobilized lipase lipozyme in a water bath with thermostat control vibration shaking table at 60 °C for 24 hours, the reaction mixture was further concentrated with the help of a rotary evaporator that provided a residue that was subjected to purification with column chromatography using chloroform : methanol as eluent to provide the desired compound **3.**

Synthesis of fourth sugar ester-based mangiferin derivative, using raw mangiferin with (E)-3-(4-hydroxy-3-methoxyphenyl)acrylic acid and DMSO in the presence of immobilized lipase lipozyme in a water bath with thermostat control vibration shaking table at 60 °C for 24 hours, the reaction mixture was further concentrated with the help of a rotary evaporator that provided a residue that was subjected to purification with column chromatography using chloroform : methanol as eluent to provide the desired compound **4.**

2.7. Mangiferin analogues as anti-inflammatory agents

In 2014, S. Mahendran et al.[96] synthesized the most active free radical scavenging mangiferin derivatives **1-4** by modification in the structure of mangiferin and developed benzoylation, acetylation, methylation, and benzylation-based novel mangiferin derivatives as anti-inflammatory, antioxidants, and analgesic agents **1-4**, represented in Scheme 7.

Using the benzoylation of mangiferin, in the solution of mangiferin is mixed with benzoyl chloride and pyridine, and the reaction mixture reacts with basic alumina at room temperature.



Scheme 7. Synthetic route of mangiferin derivatives[96]

Then the further reaction mixture is kept at 70 °C for 30 minutes, and then the reaction product is cooled to room temperature, which was extracted with

dichloromethane (CH_2Cl_2) three times. The combined extracted product is washed with water, dried over sodium sulfate (Na_2SO_4), and concentrated with the help of a rotary evaporator to remove solvent, then crystallized with (ethyl acetate : petroleum ether : ethanol), which is subjected to the desired compound, tribenzoyl mangiferin (**1**).

With the help of the benzylation of mangiferin in the solution of mangiferin, dry DMF, benzyl chloride ($C_6H_5CH_2Cl$), was reacted in the presence of K_2CO_3 at 60 °C for 10 hours with continuous stirring. The resulting reaction mixture was kept for evaporation, which gave a residue that was further purified with the help of column chromatography, and the fraction was concentrated to provide the desired compound, benzyl mangiferin (**2**).

Mangiferin was subjected to acetylation; a solution of mangiferin in pyridine was reacted with acetic anhydride with continuous stirring at 40 °C for 36 hours. Then the resulting reaction mixture was washed with water and extracted with chloroform soluble fraction then the resulting reaction mixture was kept for evaporation, which gave a residue that was further purified with the help of column chromatography, and the fraction was concentrated to provide the desired compound, acetyl mangiferin (**3**).

Methylation of mangiferin: in a solution of mangiferin, acetone was reacted with dimethyl sulphate and K_2CO_3 at 25 °C for one week, the reaction mixture was further concentrated with the help of a rotary evaporator that provided a residue that was subjected to purification with column chromatography using chloroform:methanol as eluent to provide the desired compound, methyl mangiferin (**4**)**.**

2.7.1. Biological activity

2.7.1.1. Antioxidant activity

The antioxidant activity of solutions containing varying amounts of mangiferin and its derivatives. In DPPH, ABTS, H2O2, and nitric oxide in-vitro test models, mangiferin showed very potent antioxidant activity with IC_{50} values of 1.72±0.07, 0.09±0.01, 8.39±1.09, and 32.58±0.34 µg/ml, respectively in Table 5. In every approach, benzoyl and acetyl mangiferin (**1, 3**) showed strong to moderate activity. In lipid peroxidation, p-NDA, and deoxyribose assays, benzoyl and acetyl mangiferin (**1, 3**) demonstrated superior efficacy compared to mangiferin. Only benzoyl mangiferin shown strong activity in the alkaline DMSO method. Compared to the standards, benzoyl mangiferin exhibited superior activity in the p-NDA, lipid peroxidation, and alkaline DMSO method. The activity benefited with the substitution of acetyl and benzoyl groups for mangiferin. These findings led to the selection of acetyl and benzoyl mangiferin (**1, 3**) in addition to mangiferin for comparison of their in-vivo and antiinflammatory properties.

Table 5. The in-vitro anti-oxidant activity of mangiferin and its derivatives[96]

Sr. No	Compunds	IC_{50} values±SEM (mcg/ml) by models							
		D.P.P.H.	A.B.T.S.	Deoxyribose	p-NDA	H_2O_2	Nitric oxide	Lipid peroxidation	Alkaline DMSO
1.	Mangiferin.	1.72±0.17	0.09±0.02	502.20±35.10	106.84±0.17	8.39±1.09	32.58±0.14	433.20±4.18	>1000
2.	1	23.80±0.89	0.65±0.02	87.58±2.21	24.13±1.05	23.57±0.34	52.67±1.30	8.90±0.98	152.30±3.63
3.	2	>1000	2.41±0.08	>1000	>1000	215.02±3.11	>1000	>1000	>1000
3.	3	36.47±0.81	3.71±0.14	406.30±2.85	31.53±3.72	81.23±1.05	>1000	29.80±1.27	>1000
4.	3	>1000	2.23±0.06	>1000	>1000	>1000	>1000	>1000	>1000
5.	Ascorbic. acid	4.92±0.38	11.25±0.49	-	>1000	193.45±2.30	-	-	>1000
6.	Rutin	8.91±0.15	0.52±0.041	-	205.54±3.45	32.35±1.02	65.21±2.97	-	>1000
7.	BHA	-	-	83.46±40	-	22.16±0.56	-	110.02±3.41	-

2.7.1.2. Anti-inflammatory activity

The carrageenan-induced paw edema in rats was used as a model to investigate the in vivo anti-inflammatory activity of mangiferin and benzoyl mangiferin (**1**) had considerable efficacy at a dose of 20 mg/kg for measures ranging from 30 to 360 minutes in rats with paw edema generated by carrageenan, as compared to the control group. Table 6. demonstrated a significant reduction in paw edema after 120, 180, and 360 minutes for mangiferin, benzoyl mangiferin (**1**), and acetyl mangiferin (**3**) at 10 mg/kg and 20 mg/kg, respectively. Nevertheless, compared to the tested samples, the normal dose of diclofenac (20 mg/kg) likewise yielded comparable and superior outcomes. After 360 minutes of tests, the percent protection was discovered to be 28.17 to 37.09.

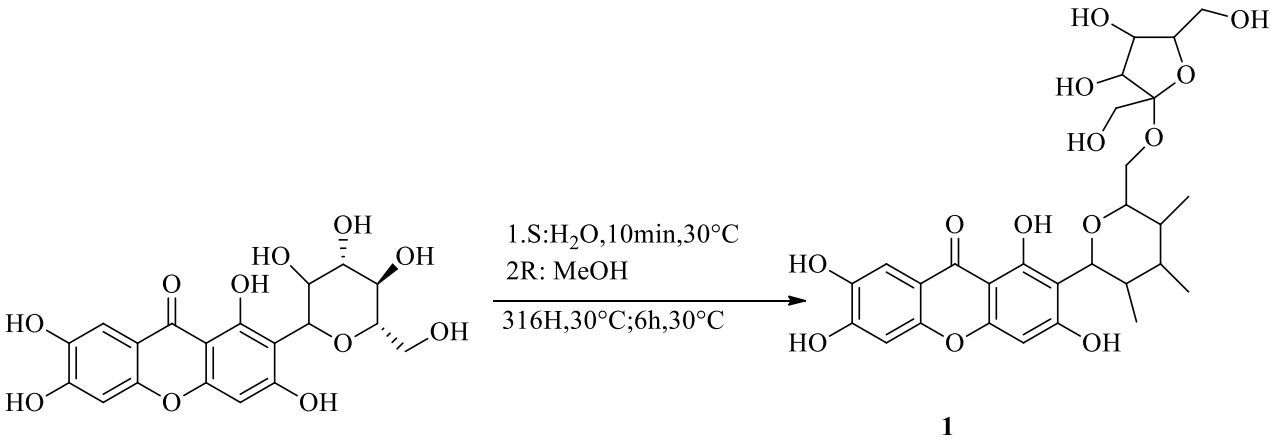
Table 6. The in vivo anti-inflammatory activity of mangiferin and its derivatives against carrageenan-induced paw edema in rats[96]

Sr. No	Treatment Groups	Dose - mg/kg	Paw volume in ml after minutes					
			0	30	60	120	180	360
1.	Control Group	Control	0.84±0.02	1.63±0.04	1.77±0.05	1.90±0.07	1.96±0.07	2.13±0.06
2.	Mangiferin	10	0.91±0.04	1.51±0.0	1.60±0.06	1.56±0.07	1.52±0.08	1.48±0.08
		20	0.98±0.08	1.39±0.04	1.46±0.04	1.43±0.06	1.38±0.05	1.34±0.04
3.	Benzoyl mangiferin (**1**)	10	0.98±0.05	1.55±0.04	1.57±0.04	1.59±0.04	1.55±0.09	1.52±0.05
		20	1.00±0.06	1.40±0.04	1.40±0.06	1.41±0.04	1.36±0.03	1.37±0.05
4.	Acetyl mangiferin (**3**)	10	0.95±0.05	1.58±0.03	1.67±0.06	1.60±0.07	1.55±0.07	1.53±0.06
		20	1.02±0.03	1.51±0.06	1.55±0.04	1.57±0.01	1.45±0.08	1.42±0.07
5.	Diclofenac (**std**)	20	0.89±0.04	1.22±0.05	1.25±0.05	1.30±0.03	1.16±0.02	1.13±0.03

Note*: According to Dunnet's test, values are expressed as mean±S.E.M. for groups of six animals each; differences between the control and treatment groups are statistically significant at aP<0.001, bP<0.01, and cP<0.05.*

2.8. Synthesis of glycosylated β-D-glucopyranosyl-mangiferin

In 2015, Bingfang He, Xueming Wu, Jianlin Chu, Bin Wu, Sen Zhang, Pingkai Ouyang. *et al.*[97] synthesized beta-d sugar-based mangiferin derivative **1** by modification in the structure of mangiferin with the help of glycosylation via biotransformation in the presence of arlhrobacler nicolianae and dextrasucrase depicted in Scheme 8.



Scheme 8. Synthesis of glycosylated β-D-glucopyranosyl-mangiferin[97]

2.9. Synthesis of polysulfated mangiferin derivatives

In 2011, Madalena M. M. Pinto *et. al.*[98] synthesized two polysulfated mangiferin derivatives (**1-3**) by modification in the structure of mangiferin with the help of sulfation, depicted in Scheme 9. Synthesis of polysulfated mangiferin derivatives (**1-3**), produced by sulfating commercially available mangiferin with 4, 8, and 6 equivalent/OH, respectively, of triethylamine sulfur trioxide adduct in dimethy-lacetamide at 65 °C for 24 hours that provide desired compounds (**1-3**).

2.9.1. Biological activity

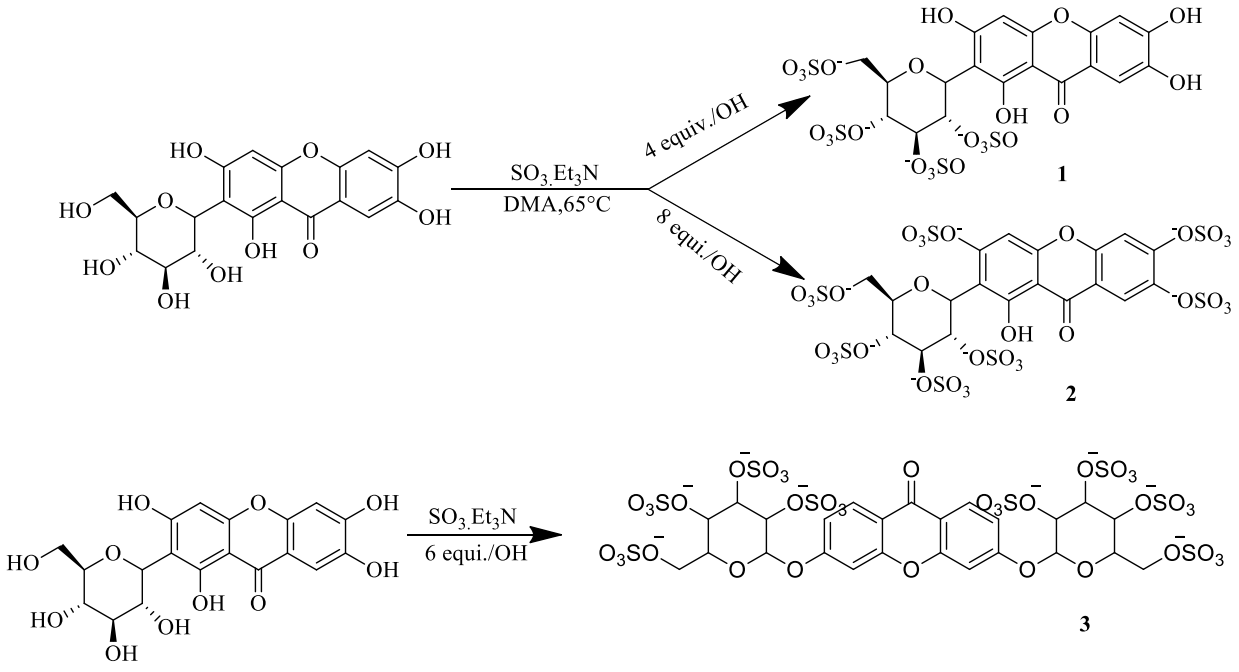
The anti-coagulant activity of solutions containing varying amounts of polysulfated mangiferin derivatives (**1-3**) is shown in Table 7. The anti-coagulant effect of the

polysulfated mangiferin derivatives was examined in vitro using prothrombin (PT), activated partial thromboplastin (APTT), and thrombin time (TT) tests on human plasma. To investigate the impact of the sulfate group on the anti-coagulant activity, mangiferin sodium sulfate was also taken into consideration.

Table 7. Anticoagulant activity of polysulfated derivatives of mangiferin[98]

Sr. No	Compounds group	$APTT_2$	PT_2	TT_2
1.	1	0.39	nt	nt
2.	2	2.21	1.60	1.96
3.	3	0.06	0.71	na

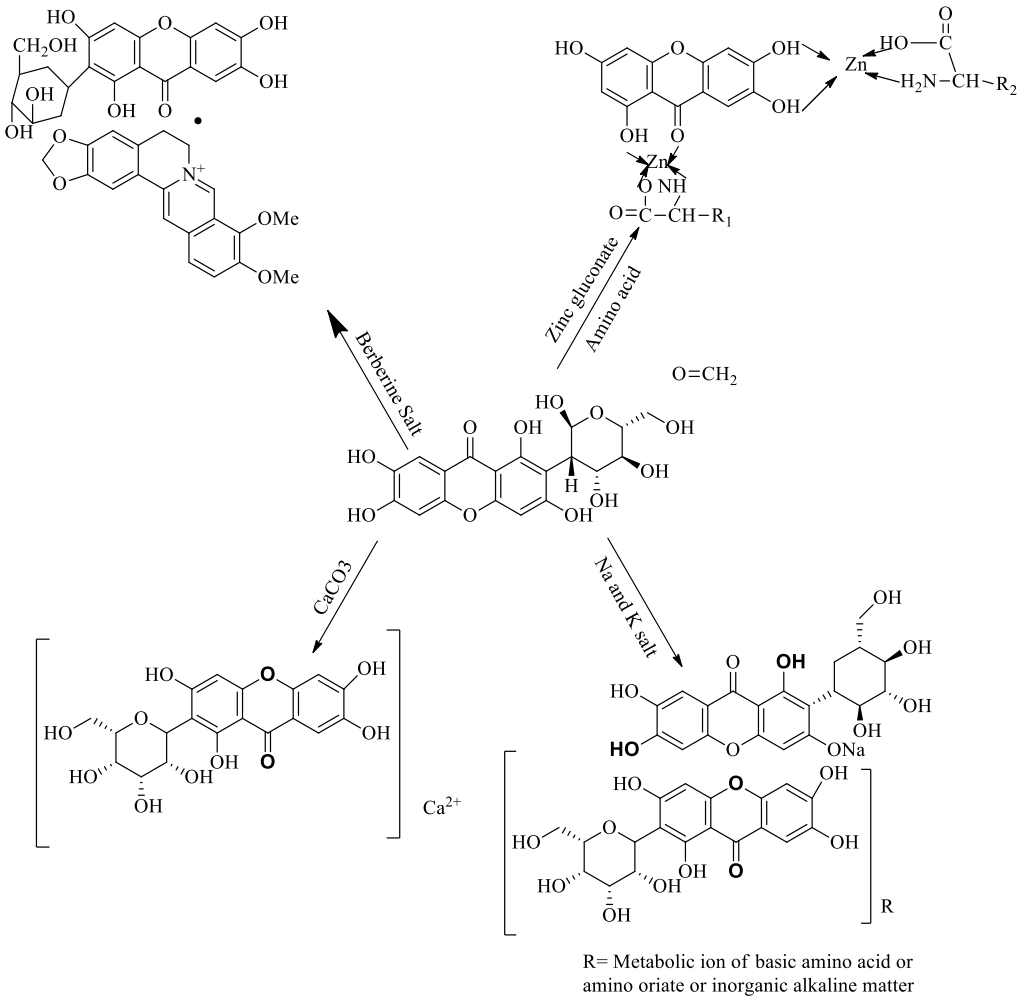
Concentration values expressed in 10^{-3} M are the means of three separate studies, with a standard deviation of less than 10%. Heparin is the positive control; $APTT_2$=0.4U/mL, PT_2=1.9U/mL, and TT_2=0.2U/mL, nt = not tested, na = not active (P>0.05).at $5.00x10^{-3}$ M.



Scheme 9. Synthesis of sulfated derivatives of mangiferin[98]

2.10. Synthesis of calcium and zinc salt-based mangiferin derivatives

In 2012, Teng, H., Wu, W., and Xu, G. *et. al*,.[99] synthesized calcium and zinc salt-based mangiferin derivatives **1-4** as insulin sensitizer and oral hypoglycemics, as depicted in Scheme 10. A solution of mangiferin monosodium is heated to 60 °C in order to prepare the calcium salt of mangiferin.



Scheme 10. Synthetic route and Complexation reaction of Mangiferin derivatives[99]

2.10.1. Biological activity

In order to enhance the sensitivity of insulin to beta cells of the pancreas, calcium-salt-based mangiferin derivatives have shown good activity as antidiabetic agents.

2.11. Synthesis of novel esterified and alkyl amine mangiferin analogues

In 2022, Krishna R. Gupta, mohan H. Patil, milind J. Umekar *et. al.*,[100] synthesized novel mangiferin derivatives **1-12** as antioxidants and anticancer agents, depicted in figure 3, by modification in the structure of mangiferin, in efforts to enhance antioxidant and anticancer activity.

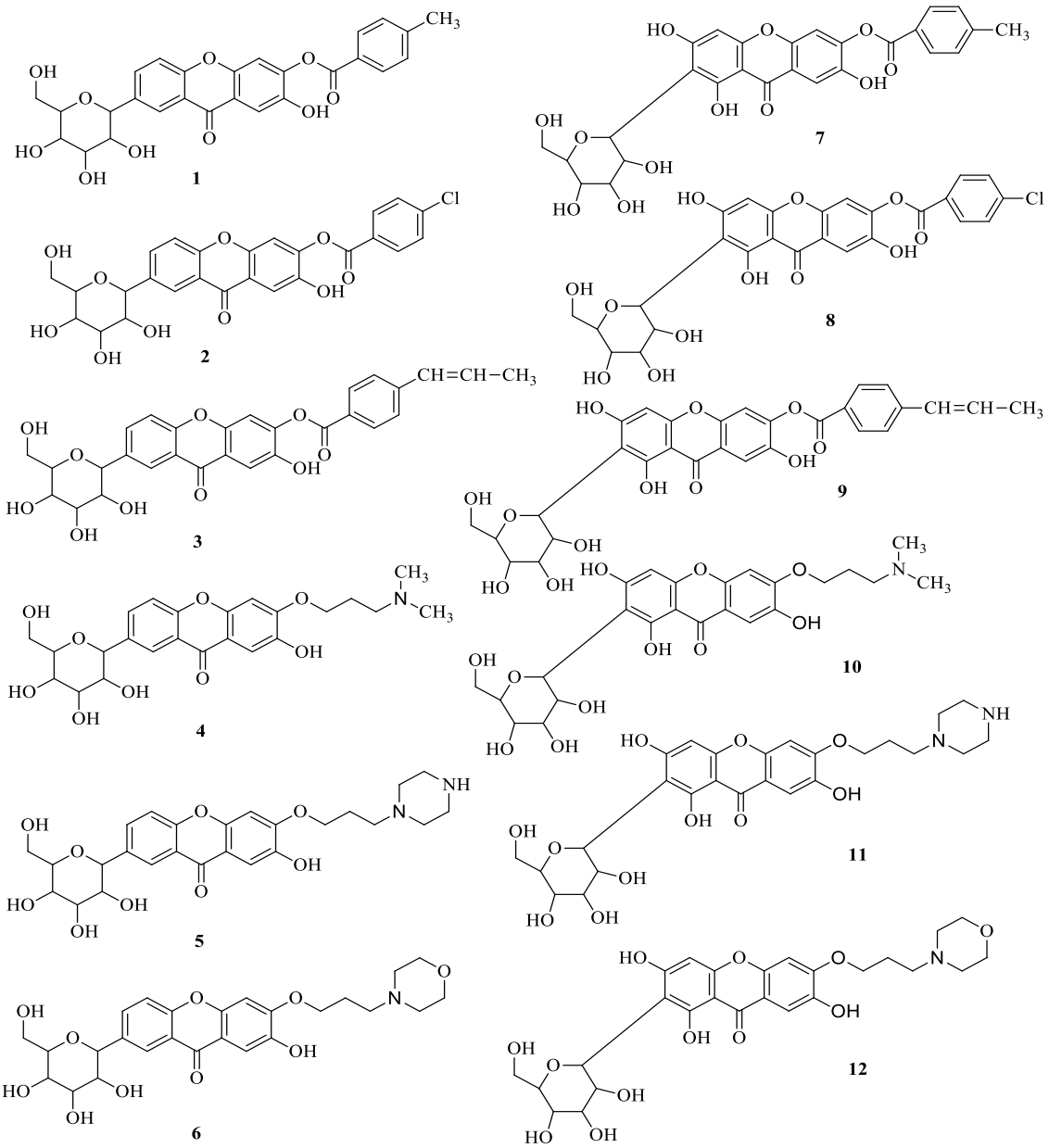


Figure 3. structure novel esterified and alkyl amine mangiferin derivatives[100]

Table 8. Patented literature

Sr. No	Tittle as Biological activity	Application No./ Patent No.	Publication Date	Inventors	References
1.	Analgesic	KR2014/001252	10/30/2014	Kim Dong Hyun, *et. al.*	[101]
2.	Anthelminthic	EP2009/054349	10/15/2009	De Kochko Alexandre, *et. al.*	[102]
3.	Anti-allergic	JP2009/066203	04/01/2010	Fujifilm Corporation, *et. al.*	[103]
4.	Anti-amoebic	09/728051	09/02/2003	Winter Rolf W, *et. al.*	[104]
5.	Anti-atherosclerosis	14/547537	05/21/2015	Deshpande Jayant, Ghanam Khadija, *et. al.*	[105]
6.	Anti-bacterial	13/440446	07/26/2012	Gupta Shyam K. *et. al.*	[106]
10.	Anti-inflammatory	JP2007000187837	02/05/2009	Matsuda Hideaki, *et. al.*	[107]
13.	Anti-proliferative	13/023594	06/30/2011	Hoffmann Erika, Horres Roland, Faust Volker, *et. al.*	[108]
15.	Arthritic	12/865995	01/06/2011	Park Dong-suk, *et. al.*	[109]
23.	Prevent osteoporosis	PCT/WO2008061480A1	23/05/2008	Guang'ai Xu, *et. al.*	[110]
24.	Anticancer	KR WO/ US1997/006988	08/03/2012	Bingfang He, Xueming WuJianlin, *et. al.*	[111]
23.	Prostate Cancer	CN104013611B	17/06/2014	Liu Dan, Liu Yidan, Qi Meifeng, *et. al.*	[112]
24.	Anticancer	CN103755692A	29/01/2014	Zhou Rongguang, *et. al.*	[113]
23.	AMPK activator as Anticancer	WO2010145192A1	03/06/2010	Tenghou Lei, Wu Wei, *et. al.*	[114]

3. Conclusion

The versatile biological and pharmacological activities of mangiferin and its derivatives in a range of medicinal situations, including cancer, diabetes, hypertension, depression, microbial infection, etc., have attracted a great deal of attention from researchers. Mangiferin shares a molecule that can be easily modified chemically, and by adding small chemical modifications, their pharmacological activity can be varied, even their efficiency. A significant amount of research work is in progress, and many patent applications have been filed for the physiologically active substances that contain the pharmacophore mangiferin. Researchers are encouraged by some of the most potent mangiferin derivatives to find new, safer anticancer mangiferin analogues. The use of Mangiferin analogues as anticancer, anti-inflammatory, neuroprotective, antidiabetic, analgesic, antimalarial, anticonvulsant, antioxidant, antimicrobial, antipsychotic, anticoagulant, and antihypertensive actions, among other things, has also been the subject of some recent primary findings.

Conflict of interest

The authors declare no conflict of interest

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