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Aqueous hydrotropes: An efficient and reusable catalyst for the synthesis of 3-carboxy-coumarin motifs at room temperature

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RESEARCH ARTICLE

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ABSTRACT

The coumarin moiety plays an important role in the large number of natural products possessing different kinds of biological diversity. Coumarin carboxylic acids show a wide range of biological activities in the pharmaceutical and agricultural fields. Knoevenagel condensation is one of the important reaction pathways for synthesizing coumarin derivatives, and many methodologies have been developed to synthesize this class of compounds. A more environmentally friendly method of synthesizing 3-carboxy coumarins has been successfully carried out using 50% aqueous NaPTS hydrotropes at room temperature, along with various substituted 2-hydroxy benzaldehydes and Meldrum's acid. This process involves Knoevenagel condensation followed by intramolecular cyclization, providing better product yields (78-95%).

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1. Introduction

Nowadays, researchers are more interested in synthesizing heterocyclic compounds using greener approaches. Several researchers have been attracted toward green chemistry as a means of discovering new chemical organic routes that are more efficient and environmentally friendly. To minimize environmental pollution, the use of less toxic chemicals, the use of environmentally friendly protocols, and the use of water as solvents are the main choices of researchers to synthesize biologically active heterocyclic compounds [1]. Compounds containing coumarin moieties have great synthetic utility in organic synthesis. The synthesis of coumarin and its derivatives has fascinated the interest of synthetic chemists due to its unique structural motifs, which serve as a crucial building block for a variety of natural and semi-synthetic products [2,3]. Coumarin and its derivatives have a wide range of biological effects, including antitumor [4-7], anticoagulant [8,9], antifungal [10], antibiotic [11], anti-HIV-1 [12-15], and anti-oxidant properties, *etc.* [16,17] (Figure 1). Heterocyclic compounds containing coumarins, or 3-carboxy coumarins, are a unique class of chemicals with a wide range of applications. According to the literature, these compounds are being used as synthons of a variety of natural and semi-synthetic pharmacological agents such as β-lactams [18], isoureas [19], and tetrahydropyridones [20]. In addition to these applications, these compounds are also commonly used as fluorescent probes [21] and triple oxygen sensitizers [22]. The most effective way to create 3-carboxy coumarin derivatives is to use the one-pot approach, which involves the reaction of 2-hydroxybenzaldehyde with Meldrum's acid, which proceeds via Knoevenagel condensation followed by intramolecular cyclization [23].

Various methods have been reported to synthesize carboxy coumarin derivatives from 2-hydroxybenzaldehyde and Meldrum's acid which involve the use of ammonium acetate [24], triethylbenzyl ammonium chloride (TEBAC) [25], $Yb(OTf)_3$ [26], $FeCl_3$ [27], $SnCl_2$ [28], K_3PO_4 [29], [Hmim]Tfa [30], Magnetic cellulose/gamma-Fe_2O_3/Ag nanocatalyst [31], amide-functionalized heterogeneous {[Cd_2(2-BPXG)(Fum)$_2$ (H_2O)$_2$]·

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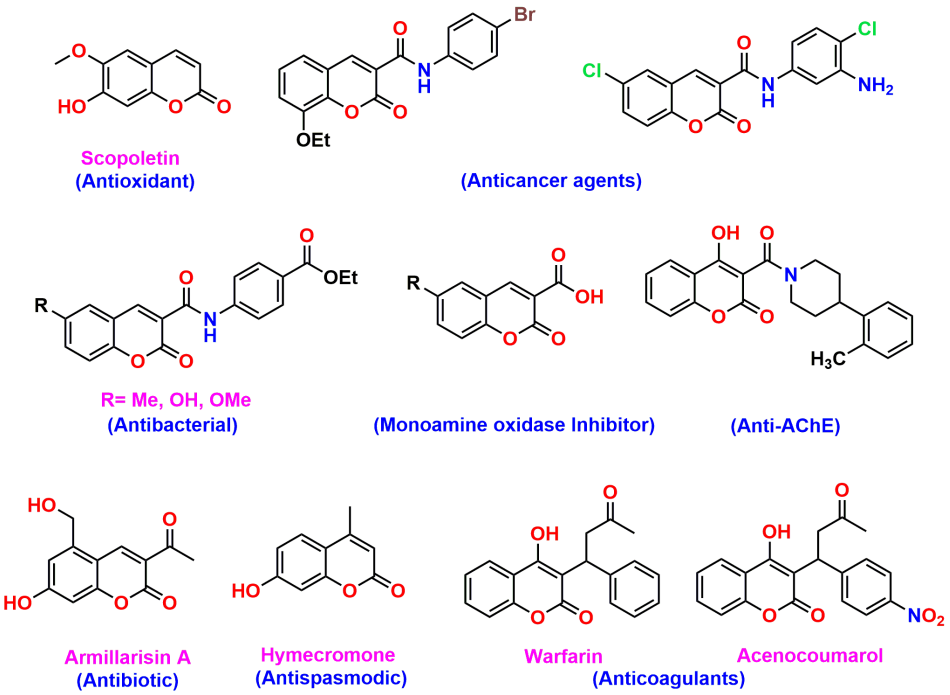
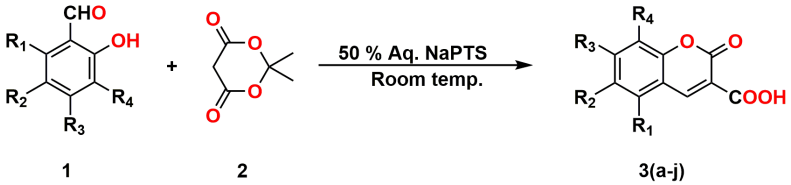


Figure 1. Some biologically active coumarin derivatives.



3a: R_1-R_4 = H
3b: R_1, R_2, R_4 = H, R_3 = NMe_2
3c: R_1, R_2 = H, R_3-R_4 = OH
3d: R_1, R_3, R_4 = H, R_2 = Cl
3e: R_1, R_3, R_4 = H, R_2 = Br
3f: R_1, R_2, R_4 = H, R_3 = OMe
3g: R_1, R_3, R_4 = H, R_2 = OMe
3h: R_1, R_3 = H, R_2, R_4 = Br
3i: Napthaldehyde
3j: R_1, R_3 = H, R_2, R_4 = Cl

Scheme 1. Synthesis of 3-carboxy coumarin derivatives.

$2H_2O\}n$ [32], extract of acacia concinna pods [33], K_2CO_3 or NaN_3 [34], extract of banana peels [35], NEt_3 [36], choline chloride/urea [37], L-lysine [38], silica sulfuric acid [39], *etc*. Synthesis of 3-carboxy coumarins using the aforementioned methods has both benefits and drawbacks, including the use of hazardous chemicals, organic solvents and reagents, severe reaction conditions, laborious work-up procedures, low yield and purification of desired products. At present, there is a great demand to overcome these demerits and to find a more beneficial protocol that utilizes the maximum principles of green chemistry. Our research group is constantly working on developing newer, greener methodologies for synthesizing heterocyclic compounds [40-42]. Currently, the low-solubility problems of organic compounds are well solved by the use of hydrotropes. Hydrotropes were first discovered in 1916 by Carl Neuberg. These are the compounds that are responsible for increasing the solubility of the hydrophobic compounds in water up to 200 times. Hydrotropes have many advantages, as they are stable to heat, air, and water and are less toxic [43]. Similarly, to the critical micelle concentration (CMC) for a surfactant, the minimal hydrotrope concentration (MHC) is the hydrotrope concentration beyond which hydrotrope aggregation is responsible for an increase in water solubility. In 1946, McKee addressed the possible use of hydrotropes in industry [44]. Hydrotropes have wide applications in pharmaceuticals, agrochemicals, health care, and household as well as in the extraction of fragrances [45]. Numerous studies have been reported on the use of aqueous hydrotropic solutions as a particular kind of alternative reaction media for the synthesis of organic compounds [46]. Upon extensive literature review, it was found that no research was done on the use of hydrotropes for the synthesis of 3-carboxy coumarins. In light of all these considerations, we have found a unique method for producing biologically potential 3-carboxy coumarins by using aqueous hydrotropes as a greener media (Scheme 1).

2. Experimental

2.1. Materials

For this experiment, all chemicals and solvents were acquired from Thermo Fisher and Sigma Aldrich with a purity greater than 98%, and no further purification was required. The known compounds were identified by comparing their melting points and spectroscopic data. The melting points are uncorrected and were obtained using the open capillary method. Using thin layer chromatography (TLC), the progress of the reaction was monitored employing Merck silica gel $60F_{254}$ plates.

Table 1. Optimization study for the synthesis of 3-carboxy coumarin derivatives *.

Entry	Catalyst concentration	Time (h)	Yield (%)
1	H_2O	6	55
2	10% Hydrotropes NaPTS	6	65
3	30% Hydrotropes NaPTS	6	75
4	50% Hydrotropes NaPTS	6	85
5	50% Hydrotropes NaBS	6	60

* Reaction condition: Salicylaldehyde (1 mmol) and Meldrum's acid (1 mmol).

2.2. Instrumentation

The characterization of the obtained products was performed using FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopic techniques. The Shimadzu IR-Affinity spectrophotometer (KBr) and PerkinElmer FT-IR spectrophotometer with an ATR attachment were used to record the infrared spectra. NMR spectra (DMSO-d_6) were recorded on a Bruker Advance Neo-500 MHz spectrometer with TMS as an internal standard.

2.3. Synthesis of 3-carboxy coumarins

A mixture of substituted salicylaldehyde (1 mmol), Meldrum's acid (1 mmol), and 50 % aqueous hydrotrope NaPTS (5 mL) was vigorously stirred at room temperature in a 25 mL round bottom flask. The progress of the reaction was tracked by TLC (Hexane: EtOAc, 80:20). Once the reaction was finished, the reaction mass was added to ice-cold water and thoroughly agitated, and the resulting solid was filtered out. The solid product was washed with water to obtain almost pure 3-carboxy coumarins. All compounds are purified by simple recrystallization from ethanol. Characterization data of some synthesized compounds are given below.

2-Oxo-2H-chromene-3-carboxylic acid (**3a**): Color: White. Yield: 85%. M.p.: 188-190 °C. FT-IR (KBr, ν, cm^{-1}): 3473, 3338, 3174, 3057 (OH), 2993, 1736 (C=O), 1676 (C=O), 1570, 1452, 1226, 1165, 1041, 831, 771. ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.36-7.40 (m, 2H, Ar-H), 7.68-7.72 (m, 1H, Ar-H), 7.86 (q, 1H, *J* = 7.7 Hz, Ar-H), 8.69 (s, 1H, C-H), 11.96 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 116.1, 117.9, 118.3, 124.9, 130.2, 134.4, 148.4, 154.5, 156.9, 164.0.

7-(Diethylamino)-2-oxo-2H-chromene-3-carboxylic acid (**3b**): Color: Orange. Yield: 95%. M.p.: 216-218 °C. FT-IR (KBr, ν, cm^{-1}): 3462, 3263, 3111 (OH), 2984, 1736 (C=O), 1668 (C=O), 1577, 1452, 1357, 1267, 1084, 808, 775. ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 1.13 (t, 6H, *J* = 7.0 Hz, CH_3), 3.47 (q, 4H, *J* = 7.0 Hz, CH_2), 6.56 (s, 1H, Ar-H), 6.78 (q, 1H, *J* = 9.0 Hz, Ar-H), 7.63 (d, 1H, *J* = 9.0 Hz, Ar-H), 8.57 (s, 1H, Ar-H), 12.50 bs (1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 12.2, 44.2, 95.8, 107.1, 109.9, 125.4, 127.9, 131.7, 149.3, 152.8, 157.7, 159.4, 164.3.

6-Chloro-2-oxo-2H-chromene-3-carboxylic acid (**3d**): Color: White. Yield: 78%. M.p.: 118-120 °C. FT-IR (KBr, ν, cm^{-1}): 3437, 3255, 3165 (OH), 3038, 2943, 1734 (C=O), 1670 (C=O), 1489, 1338, 1201, 1085, 821, 709. ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.46 (1H, *J* = 8.8 Hz, Ar-H), 7.75 (q, 1H, *J* = 8.7 Hz, Ar-H), 8.01 (s, 1H, Ar-H), 8.67 (s, 1H, Ar-H), 11.44 (bs, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 118.1, 119.3, 119.6, 128.4, 128.9, 133.6, 146.9, 153.0, 156.2, 163.7.

6,8-Dibromo-2-oxo-2H-chromene-3-carboxylic acid (**3h**): Color: White. Yield: 80%. M.p.: 206-208 °C. FT-IR (ATR, ν, cm^{-1}): 3590, 3524, 3065 (OH), 1763(C=O), 1634(C=O), 1549, 1449, 1250, 1159, 864, 741. ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 8.14 (d, 1H, *J* = 2.2 Hz Ar-H), 8.19 (d, 1H, *J* = 2.2 Hz Ar-H), 8.50 (s, 1H Ar-H), 12.40 (bs, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 109.8, 116.0, 121.1, 131.1, 137.4, 144.4, 149.9, 155.6, 163

6,8-Dichloro-2-oxo-2H-chromene-3-carboxylic acid (**3j**): Color: White. Yield: 88%. M.p.: 200-202 °C. FT-IR (ATR, ν, cm^{-1}): 3461, 3075 (OH), 1747 (C=O), 1644 (C=O), 1556, 1456, 1250, 998, 803, 616. ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.91 (d, 1H, *J* = 2.4 Hz, Ar-H), 7.94 (s, 1H, *J* = 2.3 Hz, Ar-H), 8.62 (s, 1H, Ar-H), 12.47 (bs, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 120.3, 120.5, 120.6, 127.9, 128.2, 132.6, 146.3, 148.7, 155.0, 163.4.

3. Results and discussion

3.1. Synthesis of 3-carboxy coumarins

The synthesized products were characterized using FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopic techniques. All known compounds exhibited physical and spectroscopic data consistent with those previously reported in the literature [34]. The IR absorption band at 3107 to 3590 cm^{-1} indicates the presence of a hydroxyl (OH) group in the synthesized organic compounds. The findings of different absorption peaks at 1634 to 1676 cm^{-1} indicate the presence of carbonyl groups (C=O) associated with the carboxyl group (COOH) in organic compounds. The IR bands at 1734 to 1763 cm^{-1} indicate the stretching vibration frequency of carbonyl groups (C=O) of the cyclic ester within the organic compounds. The observed peak in the ^{1}H NMR spectra of the compounds ranging from δ 11.44 to 12.50 ppm broad signal indicates the presence of the hydroxyl (OH) group of the carboxyl moiety present within the organic compounds. In the ^{13}C NMR spectrum, two distinct peaks appeared between δ 163.0 and 164.3 ppm indicating the presence of carboxyl groups. Furthermore, peaks between δ 155.0 and 156.9 ppm were observed, corresponding to the carbonyl of lactone in the coumarin moiety. These findings are closely aligned with data from the literature [47].

A straightforward, clean, and energy efficient protocol is reported that involves one-pot synthesis of a series of biologically active 3-carboxy coumarins involving 50% aqueous hydrotropes as medium. Initially, our investigation started with the selection of suitable hydrotropes for the present work. Among the different hydrotropes, sodium *p*-toluene sulfonate (NaPTS) is the most attractive as it is easily available and stable to both air and moisture. As a solvent, we decided to utilize a 50% aqueous solution of NaPTS because most organic molecules can be sufficiently dissolved at this concentration. In the present work, salicylaldehyde (1 mmol) and Meldrum's acid (1 mmol) were chosen as the starting materials for the model reaction. These ingredients were mixed with 5 mL of water in a 25 mL round bottom flask and the reaction was carried out at room temperature. The progress of the reaction was monitored by using TLC (Hexane: EtOAc, 80:20). After 6 hours, the reaction yield was found to be 55%. It should be noted that by adding 10% NaPTS hydrotrope, the yield of the product increased to 65% at room temperature. Taking this into consideration, we continue our study by increasing the percentage of hydrotrope and found that the yield of the product was 75 for 30% of aq. hydrotrope and 85 for 50% of aq. hydrotrope at room temperature for 6 hours. We also found that 50% of sodium benzene sulfonate (NaBS), which slightly increased the product yield to 60%, was not suitable for further investigation. The optimum reaction condition was found based on these findings, as shown in Table 1. The overall relevance of the 50% of aq. The NaPTS hydrotrope as a reactant framework was analyzed with various substituted salicylaldehyde and Meldrum's acid to synthesize a number of 3-carboxy coumarin derivatives under streamlined conditions.

Table 2. Synthesis of 3-carboxy coumarin derivatives in aq. hydrotrope at room temperature.

Entry	Aldehyde	Product	Yield (%)	Melting point (°C)		Reference
				Found	Reported	
1	Salicylaldehyde	3a	85	188-190	188-190	[28]
2	4-(*N*,*N*-diethyl amino)-2-hydroxybenzaldehyde	3b	95	216-218	212-214	[35]
3	2,3,4-Trihydroxybenzaldehyde	3c	87	190-192	190-192	[35]
4	5-Chloro-2-hydroxybenzaldehyde	3d	78	118-120	116-118	[39]
5	5-Bromo-2-hydroxybenzaldehyde	3e	78	198-200	194-196	[39]
6	4-Methoxy-2-hydroxybenzaldehyde	3f	91	192-194	193-194	[34]
7	5-Methoxy-2-hydroxybenzaldehyde	3g	80	198-200	198-200	[34]
8	3,5-Dibromo-2-hydroxybenzaldehyde	3h	80	206-208	206-208	[34]
9	2-Hydroxynapthaldehyde	3i	80	234-236	236-237	[30]
10	3,5-Dichloro-2-hydroxybenzaldehyde	3j	88	200-202	199-202	[34]

Table 3. Comparison of our results with previously reported catalysts in water of compound **3a**.

Entry	Catalyst	Condition	Time (h)	Yield (%)	Reference
1	TEBAC, H_2O	60 °C	6	78	[12]
2	$SnCl_2{\cdot}2H_2O$	80 °C	1	80	[15]
3	K_2CO_3/NaN_3, H_2O	Room temp.	20	92	[21]
4	$Et_3N{\cdot}H_2O$	60 °C	6	90	[23]
5	50% Aq. NaPTS	Room temp.	6	85	Current work

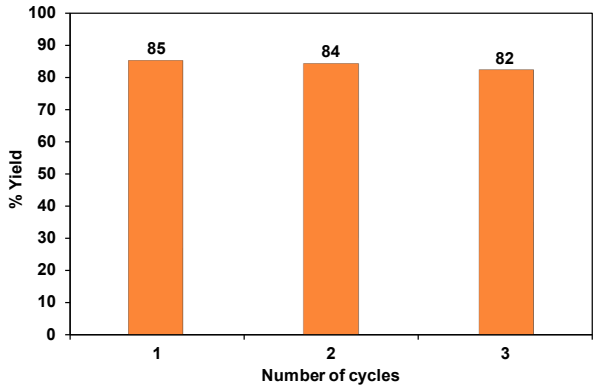
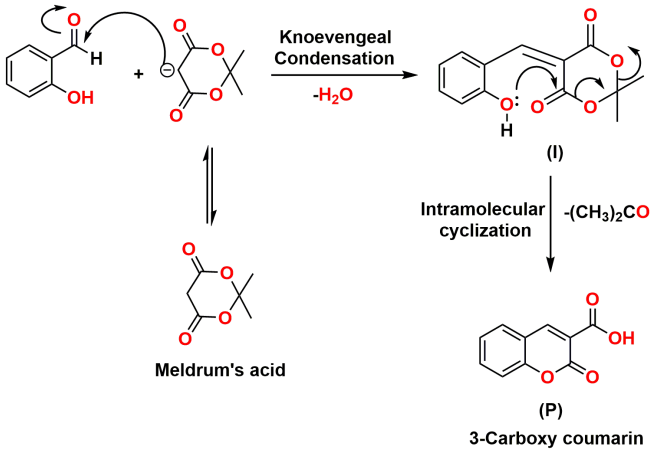


Figure 2. Reusability test of aqueous hydrotropes for the synthesis of compound 3a.



Scheme 2. Plausible mechanism of the micelles promoted the synthesis of 3-carboxy coumarins using aqueous hydrotrope.

In all cases, 3-carboxy coumarins were obtained with excellent yields (72-92%) using various substituted salicylaldehyde's as shown in Table 2. In addition, all reactions were completed in the short reaction time. The synthesized 3-carboxy coumarin derivatives were characterized by FT-IR and NMR (^1H and ^{13}C) spectroscopy.

3.2. Reusability of catalyst

In addition, an investigation was conducted to determine the reusability of 50% of the aq. NaPTS hydrotrope as a catalytic framework. It was discovered that 50% of aq. NaPTS hydrotrope catalytic framework could be reused successfully in subsequent responses up to three times. The product was filtered once the reaction was complete and the filtrate was subsequently used for the synthesis of compound **3a**. Better to excellent yields were obtained with compound **3a** (82-85%) as shown in Figure 2. The reusability of 50% of aq. NaPTS hydrotrope as a catalytic system at room temperature has successfully reached the goal of green chemistry. The 50% of aq. NaPTS hydrotrope catalytic framework was found to be successfully reused in subsequent responses up to three times to achieve better to excellent yields.

To show the benefits of this protocol, previous protocols in water and their yields for the synthesis of 3-carboxy coumarins are summarized in Table 3. Most of the protocols used for the synthesis of 3-carboxy coumarins involved the condensation of substituted salicylaldehyde and Meldrum's acid with the use of external metals and expensive reagents. In the current protocol, we have demonstrated that 50% aqueous NaPTS hydrotrope could be converted into a valuable and environmentally friendly catalytic medium in the synthesizing of newer heterocyclic compounds that benefit not only humans but also the environment. Furthermore, the current protocol is almost capable of reducing the factors that contribute to environmental problems.

Characterizations of the obtained products were performed using ^{1}H and ^{13}C NMR techniques. Knoevenagel condensation of substituted salicylaldehyde's with Meldrum's acid produces an intermediate (I), which is then cyclized intramolecularly. This method can be used to describe the production of 3-carboxycoumarin (P). Initially, in the aqueous solution of hydrotrope, the carbanion formed from Meldrum's acid attack on the carbonyl carbon of the salicylaldehyde followed by the loss of water molecules leads to the formation of intermediate (I), as shown in Scheme 2.

4. Conclusion

The present study introduced a practical method for the synthesis of 3-carboxy coumarin using 50% aqueous NaPTS hydrotrope as a greener medium at room temperature. Furthermore, several advantages, such as column chromatography, free purification, easy isolation of the products, satisfactory yield of the products, and reusable reaction medium, make this protocol environmentally benign. The synthesized compounds were characterized using FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopic techniques.

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Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

CRediT authorship contribution statement

Conceptualization: Pavan Devidas Baviskar, Arun Dinkar Kale; Methodology: Pavan Devidas Baviskar, Swati Dnyaneshwarpuri Gosavi; Validation: Pramod Pandurang Mahulikar, Vilas Nana Mahire; Formal Analysis: Pavan Devidas Baviskar, Arun Dinkar Kale; Investigation: Pavan Devidas Baviskar, Arun Dinkar Kale; Data Curation: Pramod Pandurang Mahulikar, Vilas Nana Mahire; Writing - Original Draft: Pavan Devidas Baviskar, Arun Dinkar Kale; Writing - Review and Editing: Pramod Pandurang Mahulikar, Dipak Sharadrao Dalal; Supervision: Pramod Pandurang Mahulikar.

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