Optimization of resveratrol dimerization in a batch reactor using design of experiments methodology

21 Ružičkini dani
DANAS ZNANOST – SUTRA INDUSTRIJA
9. – 11. rujna 2026. • Vukovar • Hrvatska

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INTRODUCTION

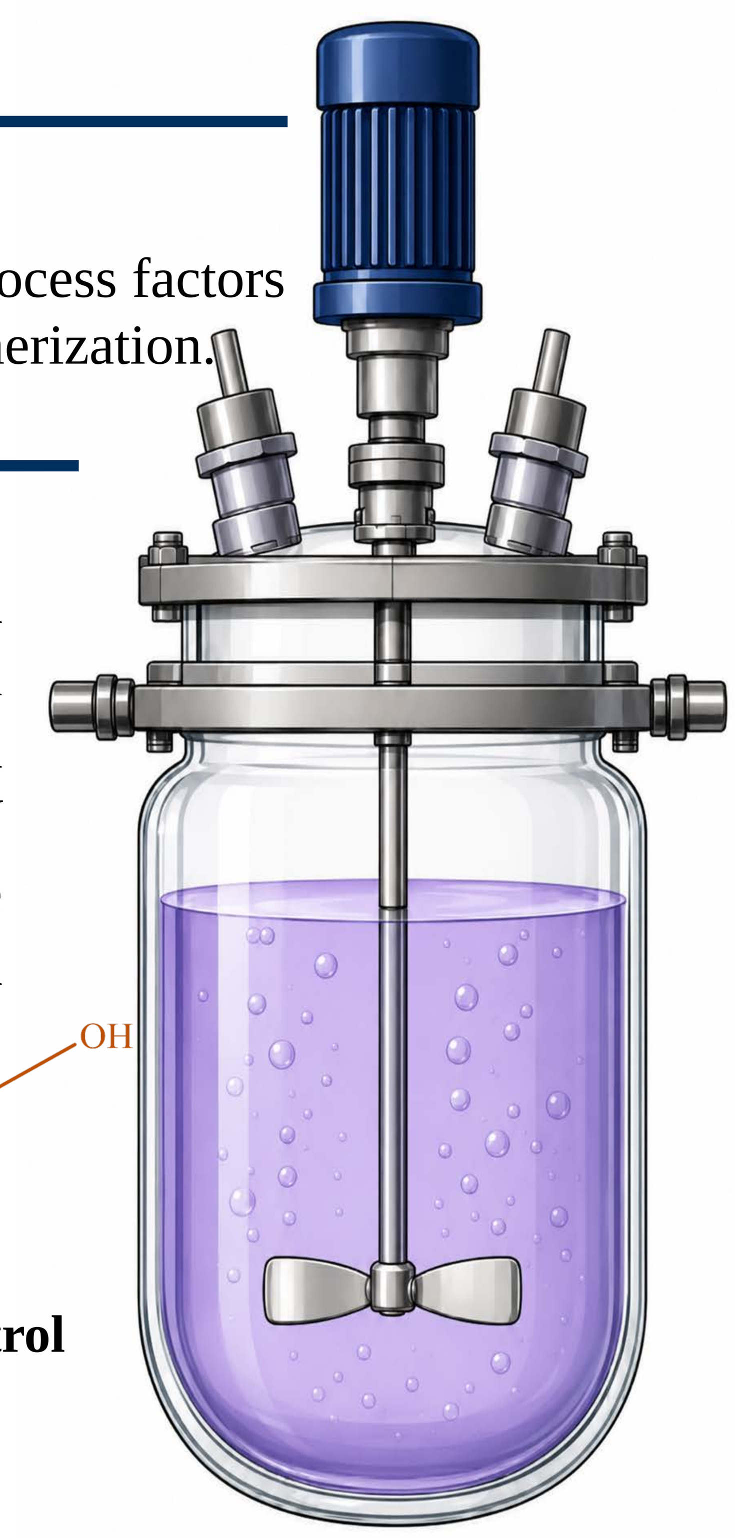
Resveratrol is a bioactive stilbene whose oxidative and photochemical coupling can generate structurally diverse dimers with potentially improved stability and biological activity. However, competing isomerization, oxidation, and oligomerization often limit dimer yield and selectivity.

In this study:

Photochemical dimerization under UV irradiation and $FeCl_3$-mediated oxidative coupling were systematically investigated in a batch reactor.

MATERIALS AND METHODS

Design of experiments (DoE) was used to identify significant process factors and operating conditions that favour selective resveratrol dimerization.



Experimental design

Two independent Box–Behnken designs with centre-point replicates were applied (Table 1a and 2a). Photochemical factors were irradiation time, resveratrol amount, and number of UV lamps; oxidative-coupling factors were resveratrol concentration, $FeCl_3$ amount, and temperature.

Photochemical dimerization

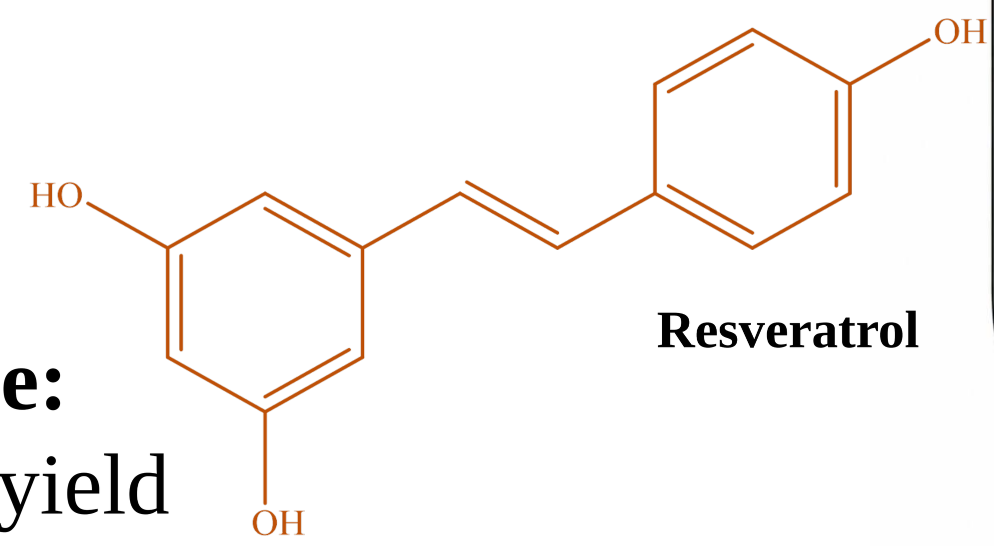
Table 1a. Factor levels used for optimization of resveratrol dimerization under UV irradiation.

Condition	Low level (−1)	Centre level (0)	High level (+1)
t (h)	1	2.5	4
$n_{resveratrol}$ (mol)	0.00001	0.0001	0.001
Number of lamps (-)	8	12	16

Oxidative coupling

Table 2a. Factor levels used for optimization of $FeCl_3$-mediated oxidative coupling.

Condition	Low level (−1)	Centre level (0)	High level (+1)
$c_{resveratrol}$ (mmol/L)	5	15	25
$FeCl_3$ (eq)	0.50	1.25	2.00
T (°C)	20	30	40



Resveratrol

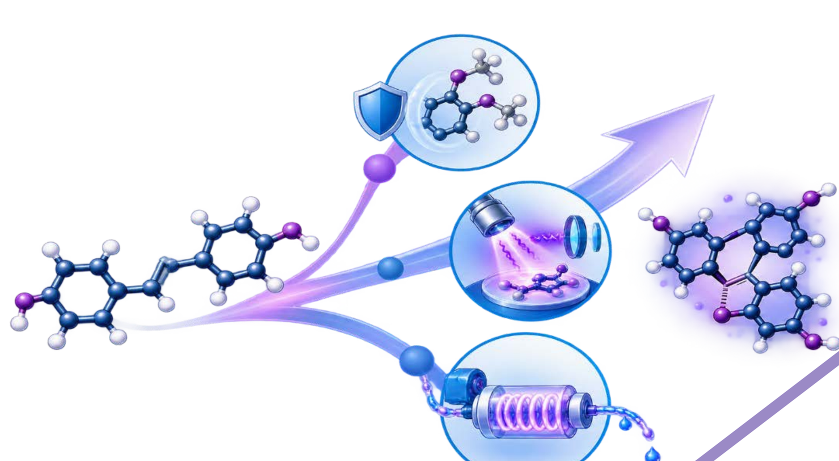
Response:
δ-Viniferin yield

RESULTS

Direct UV irradiation of unprotected resveratrol did not produce the targeted dimer under any investigated condition (Table 1b; yield: 0%). The result agrees with reports that UV exposure primarily promotes *trans*/*cis*-isomerization and singlet-oxygen-related oxidation rather than intermolecular dimerization (DOI: 10.1039/C2OB26241J; 10.1071/CH20176).
Varying substrate amount, irradiation time, and lamp number was therefore insufficient.

Table 1b. Box–Behnken experimental design and experimentally obtained product yield.

Experiment	t (h)	$n_{resveratrol}$ (mol)	Number of lamps (-)	Yield (%)
1	1.0	0.001000	12	0.00
2	4.0	0.001000	12	0.00
3	1.0	0.000001	12	0.00
4	4.0	0.000001	12	0.00
5	1.0	0.000100	8	0.00
6	4.0	0.000100	8	0.00
7	1.0	0.000100	16	0.00
8	4.0	0.000100	16	0.00
9	2.5	0.001000	8	0.00
10	2.5	0.000001	8	0.00
11	2.5	0.001000	16	0.00
12	2.5	0.000001	16	0.00
13	2.5	0.000100	12	0.00
14	2.5	0.000100	12	0.00
15	2.5	0.000100	12	0.00
16	2.5	0.000100	12	0.00
17	2.5	0.000100	12	0.00



Future studies:

- *protect hydroxyl groups,*
- *test solid-state or host-guest irradiation,*
- *use an inert atmosphere or flow photochemistry.*

$FeCl_3$ was selected as a mild, inexpensive, and readily available oxidant capable of generating phenoxy radicals and promoting oxidative C–C coupling.

ANOVA results

Significant (p < 0.05)

- $c_{resveratrol}$: p **= 0.00036**
- $FeCl_3$ amount: p **= 0.0191**
- Interaction between resveratrol concentration and temperature: p **= 0.0138**

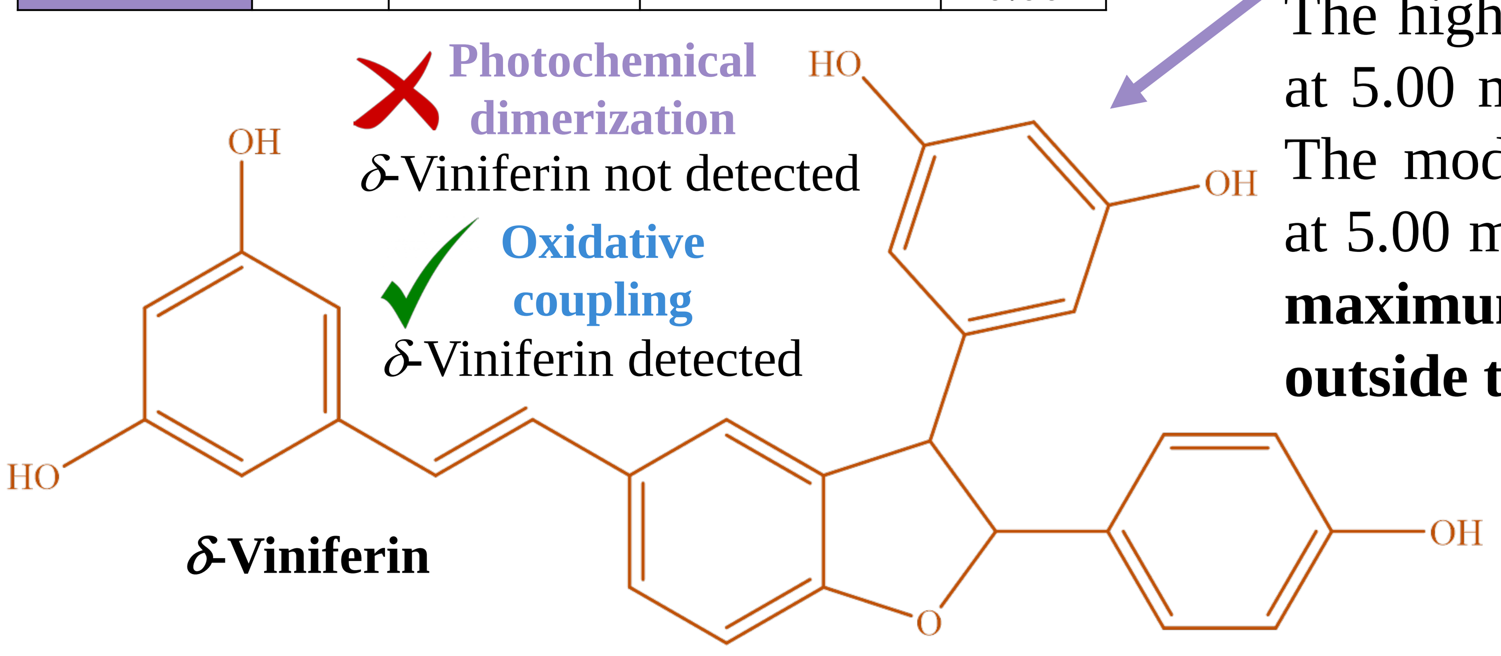
Table 2b. Box–Behnken experimental design and experimentally obtained product yield.

Experiment	$c_{resveratrol}$ (mmol/L)	$FeCl_3$ (eq)	T (°C)	Yield (%)
1	5.00	0.50	30.00	12.42
2	25.00	0.50	30.00	3.15
3	5.00	2.00	30.00	5.46
4	25.00	2.00	30.00	0.27
5	5.00	1.25	20.00	5.84
6	25.00	1.25	20.00	1.92
7	**5.00**	**1.25**	**40.00**	**16.84**
8	25.00	1.25	40.00	0.40
9	15.00	0.50	20.00	4.75
10	15.00	2.00	20.00	0.18
11	15.00	2.00	40.00	0.50
12	15.00	0.50	40.00	2.54
13	15.00	1.25	30.00	2.59
14	15.00	1.25	30.00	1.50
15	15.00	1.25	30.00	0.00
16	15.00	1.25	30.00	0.94
17	15.00	1.25	30.00	1.91

The highest experimental yield was 16.84% (Table 2b) at 5.00 mmol/L resveratrol, 1.25 eq $FeCl_3$, and 40 °C. The model predicted a boundary optimum of 16.96% at 5.00 mmol/L, 0.50 eq $FeCl_3$, and 40 °C. **No internal maximum was identified; the stationary point outside the investigated range was a saddle point.**

Photochemical dimerization
δ-Viniferin not detected

Oxidative coupling
δ-Viniferin detected



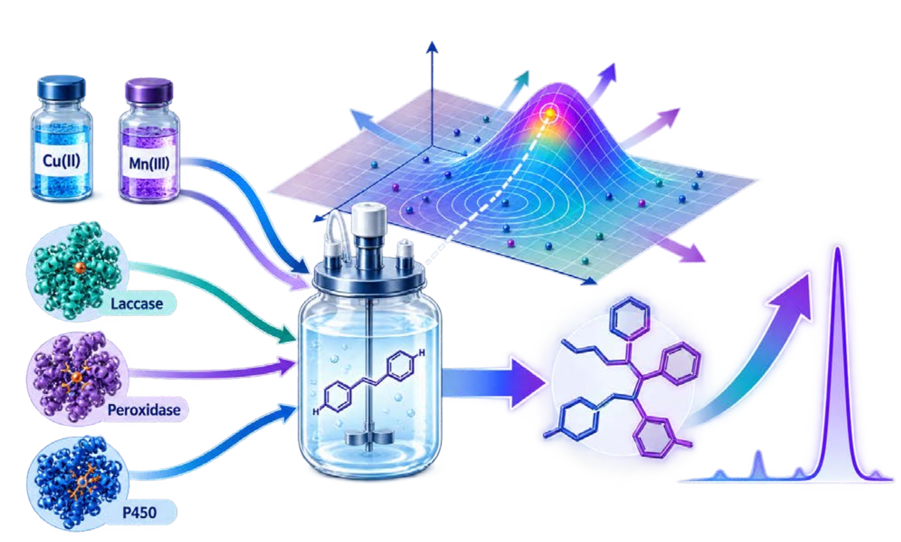
δ-Viniferin

CONCLUSION

Direct UV irradiation did not produce the targeted dimer, whereas $FeCl_3$-mediated oxidative coupling achieved a maximum experimental yield of 16.84%. DoE identified a boundary optimum that requires validation….**back to the drawing board!**

Future studies should:

- *validate the predicted optimum,*
- *expand the experimental range, and*
- *screen Cu(II) and Mn(III) salts, laccases, peroxidases, and cytochrome P450 enzyme*



This work was carried out within the project *Synthesis of Natural Active Molecules and Their Analogues in Milli- and Microflow Systems*. supported by the Croatian Science Foundation under the Research Projects Program (HRZZ UIP-2025-02-7561).