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Influence of the NSAID flurbiprofen on metabolic pathways governing lactic acid formation in *Lactobacillus pentosus* SH-114

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Abstract : Non-steroidal anti-inflammatory drugs (NSAIDs) are increasingly recognized for their unintended biochemical interactions with microbial systems. In this study, the influence of the NSAID flurbiprofen on the metabolic pathways governing lactic acid formation by *Lactobacillus pentosus* SH-114 was investigated. Batch fermentations were conducted with graded concentrations of flurbiprofen to assess changes in growth kinetics, glycolytic flux, redox balance, and end-product distribution. Flurbiprofen exposure resulted in dose-dependent modulation of lactic acid synthesis, reflected by alterations in glucose uptake rate, NAD^+/NADH turnover, and the activities of key enzymes including lactate dehydrogenase (LDH) and phosphofructokinase (PFK). Moderate concentrations enhanced lactic acid productivity by stimulating glycolytic pathway flux, whereas higher concentrations imposed metabolic stress, leading to reduced biomass formation and a diversion of carbon flow toward minor metabolites. Metabolomic profiling further revealed shifts in intracellular organic acids, suggesting that flurbiprofen perturbs membrane-associated processes and cellular energy homeostasis. These findings highlight flurbiprofen as a potent modulator of microbial fermentation physiology and provide insights into the cross-kingdom metabolic interactions between pharmaceuticals and industrially relevant laff acid bacteria. It has been found that the compound flurbiprofen antagonises the lactic acid fermentation process however, it stimulates lactic acid fermentation process and enhances the yield of lactic acid by *Lactobacillus pentosus* SH-114 to an extent of 10.309% higher in comparison to control when 15 % of molasses solution (w/v) is allowed to ferment at pH 6.1, temperature 34^0C and incubation period of 6 days.

(Keywords : NSAID flurbiprofen, molasses , lactic acid fermentation and *Lactobacillus pentosus* SH-114).

Introduction

Extensive research has shown that some organic biomolecules[1-6] are essential to promote fermentation process when incorporated into fermentation medium. A number of organic biomolecules and their derivatives has been found to support different fermentation processes[7-15] yet there are many organic biomolecules whose impact on fermentation dynamics specially lactic acid fermentation process is to be explored. NSAID flurbiprofen is a compound whose impact on lactic acid formation by *Lactobacillus pentosus* SH-114 has been made by the authors in present communication.

The influence of the NSAID flurbiprofen on metabolic pathways governing lactic acid formation in *Lactobacillus pentosus* SH-114 involves understanding both the drug's biochemical interaction and the bacterial metabolic processes. Flurbiprofen is a nonsteroidal anti-inflammatory drug (NSAID) known primarily for its anti-inflammatory effects through modulation of enzymatic pathways such as cyclooxygenase inhibition in humans. However, its effect on bacteria, particularly on *Lactobacillus species*, may extend to interactions with metabolic pathways including those related to fatty acids and potentially other biochemical pathways regulating lactic acid synthesis[16-21].

Lactobacillus pentosus, like other lactic acid bacteria, primarily produces lactic acid by fermenting carbohydrates through central metabolic routes including glycolysis, where pyruvate is converted to lactic acid via lactate dehydrogenase. Additionally, lactic acid bacteria utilize pathways like the pentose phosphate pathway and amino acid metabolism that contribute to acid production and cell acid resistance. The bacterial metabolic activity and synthesis of organic acids can be influenced by environmental factors, which may include exposure to drugs such as NSAIDs.

Studies of flurbiprofen interactions highlight its physicochemical engagement with fatty acids and changes at the molecular level, though direct effects on bacterial lactic acid production pathways are less documented. NSAIDs, including flurbiprofen, have been noted to inhibit growth of some *Lactobacillus strains*, indicating a potential impact on metabolic stability and acidogenesis. This interference may affect enzymes or metabolic intermediates involved in lactic acid formation, possibly by altering cell membrane characteristics or enzyme activities, though specific metabolic pathway changes in *Lactobacillus pentosus* SH-114 require more focused study.

Experimental

The influence of flurbiprofen on biotic production of lactic acid by *Lactobacillus pentosus* SH -114. The composition of the production medium for the biotic production of lactic acid by *Lactobacillus pentosus* SH -114 was prepared as follows :

Molasses : 15% (w/v) , Malt Extract: 1.85%
Yeast Extract : 1.85%, Peptone : 1.85%
$(NH_4)_2HPO_4$: 1.50%, $CaCO_3$: 7.5 %, pH : 6.1
Distilled water To make up 100 ml.

The pH of the medium was adjusted to 6.1 by adding requisite amount of phosphate buffer solution, and the pH was also ascertained by a pH meter.

The above composition medium represents volume of a fermentor flask, i. e., “100ml” production medium for biotic production of lactic acid.

Now, the same produciton medium for biotic production of lactic acid by *Lactobacillus pentosus* SH -114 was prepared for 99 fermentor flasks, i. e., each fermentor flask containg ‘100 ml’ of production medium.

The above fermentor flasks were then arranged in ten sets, each comprising 9 fermentor flask. Each set was again rearranged in three subsets, each comprising of 3 fermentor flasks. The remaining nine fermentor flasks out of 99 fermentor flasks were kept as control and these were also rearranged in three subsets each consisting of three fermentor flasks.

Now M/1000 solution/suspension of flurbiprofen was prepared and 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0 and 10.0 ml of this solution was added to the fermentor flasks of 1st to 10th sets respectively. The control fermentor flasks contained no flurbiprofen. Now the total volume in each fermentor flask were made up to 100ml by adding requisite amount of distil water. Thus, the concentration of flurbiprofen in 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th and 10th subsets were approximately as given below :

$A \times 1/10000 \times 10M$
$1.0 \times 1/10000 \times 10M$ to $10.0 \times 1/10000 \times 10M$
Where
A = amount of active organic molecule, i.e. flurbiprofen in ml,
$1/10000 \times 10M$ = molarity of the solution.

The fermentor flasks were then sterilized, cooled, inoculated, incubated and analysed after 2, 6 and 10 days for lactic acid[22] formed and molasses[23] sugars left unfermented.

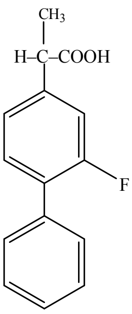
Table - 3
Biotic production of lactic acid by *Lactobacillus pentosus* SH-114 exposed to Flurbiprofen

Concentation of flurbiprofen used a x 10^{-x} M	Incubation period in days	Yield of lactic* acid in g/100 ml	Molasses substrate* left unused in g/100 ml	% of lactic acid increase in 6 days of incubation pd.
Control	2	3.369	4.059	—
(– Flurbiprofen)	6	6.654	1.269	—
	10	2.475	1.257	—
1.0 x 10^{-5} M	2	3.392	4.035	—
(+ Flurbiprofen)	6	6.703	1.220	(+) 0.736
	10	2.492	1.211	—
2.0 x 10^{-5} M	2	3.443	3.980	—
(+ Flurbiprofen)	6	6.801	1.129	(+) 2.209
	10	2.529	1.118	—
3.0 x 10^{-5} M	2	3.513	3.910	—
(+ Flurbiprofen)	6	6.941	0.982	(+) 4.313
	10	2.581	0.969	—
4.0 x 10^{-5} M	2	3.581	3.843	—
(+ Flurbiprofen)	6	7.076	0.848	(+) 6.342
	10	2.630	0.817	—
5.0 x 10^{-5} M	2	3.645	3.779	—
(+ Flurbiprofen)	6	7.203	0.720	(+) 8.250
	10	2.677	0.710	—
6.0 x 10^{-5} M**	2	3.716	3.710	—
(+ Flurbiprofen)	6	7.340***	0.589	(+) 10.309
	10	2.729	0.577	—
7.0 x 10^{-5} M	2	3.608	3.814	—
(+ Flurbiprofen)	6	7.129	0.793	(+) 7.138
	10	2.650	0.781	—
8.0 x 10^{-5} M	2	3.554	3.869	—
(+ Flurbiprofen)	6	7.021	0.910	(+) 5.515
	10	2.611	0.896	—
9.0 x 10^{-5} M	2	3.480	3.945	—
(+ Flurbiprofen)	6	6.878	1.081	(+) 3.366
	10	2.556	1.043	—
10.0 x 10^{-5} M	2	3.406	4.019	—
(+ Flurbiprofen)	6	6.729	1.198	(+) 1.127
	10	2.502	1.175	—

* Each value represents mean of three observation ** Optimum concentration of Flurbiprofen .
*** Optimum yield of lactic acid (+) Values indicate % increase in the yield of lactic acid
Experimental deviation $\pm$ 2.5 – 3.5%

Results and Discussion

Biotic production of lactic acid by *Lactobacillus pentosus* SH-114 exposed to 2-(2-fluorobiphenyl-4-yl)propionic acid (Flurbiprofen)



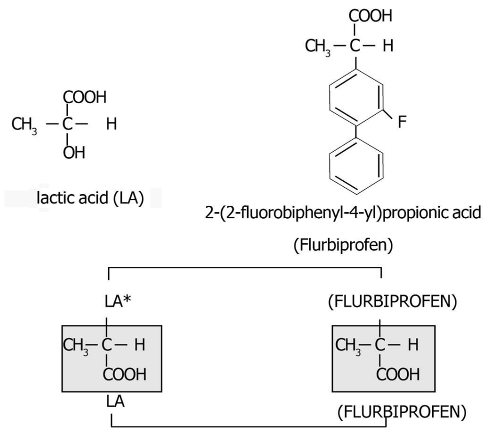
2-(2-fluorobiphenyl-4-yl)propionic acid (Flurbiprofen) ***[Compound -I]***

The data given in the table-1 shows that the compound 2-(2-fluorobiphenyl-4-yl) propionic acid (Flurbiprofen) has inhibitory effect on biotic production of lactic acid by *Lactobacillus pentosus* SH-114.

The data recorded in the table-1 shows that the addition of 2-(2-fluorobiphenyl-4-yl) propionic acid (Flurbiprofen) into the lactic acid fermentation medium enhances the production of lactic acid insignificantly. It has been observed that there is also a gradual slight increasement in the yield of lactic acid with gradual stepping up of the compound-I, i. e., 2-(2-fluorobiphenyl-4-yl) propionic acid (Flurbiprofen) till the maximum yield of lactic acid is reached which is 10.305% higher in comparison to flat bottom control fermentor flasks, i. e., 6.654 g/100 ml at 6.0×10^{-5}M molar concentration of the compound 2-(2-fluorobiphenyl-4-yl) propionic acid (Flurbiprofen) in 6 days of optimum incubation period.

The inhibitory action of 2-(2-fluorobiphenyl-4-yl)propionic acid (Flurbiprofen) may be explained from the fact that 2-(2-fluorobiphenyl-4-yl)propionic acid(Flurbiprofen) is partially structurally similar to lactic acid. Therefore, 2-(2-fluorobiphenyl-4-yl)propionic acid (Flurbiprofen) happens to be biological metabolite structural antagonist and the enzyme catalysed activity of *Lactobacillus pentosus* SH-114 is expected and supposed to be inhibited in the fermentation process.

The 2-(2-fluorobiphenyl-4-yl)propionic acid (Flurbiprofen) which happens to be structural metabolite antagonist has one end similar to the lactic acid. Thus, the compound 2-(2-fluorobiphenyl-4-yl)propionic acid(Flurbiprofen) a structural biological metabolite antagonist may perhaps prevent the proper functioning of enzyme catalysed reactions of *Lactobacillus pentosus* SH-114 but probably remains firmly attached to it by its one end. The probable structurally similar combination of 2-(2-fluorobiphenyl-4-yl)propionic acid (Flurbiprofen) with lactic acid may be illustrated as given under:



***Structural antagonist combination have one common shaded lower end.**

Therefore, 2-(2-fluorobiphenyl-4-yl)propionic acid (Flurbiprofen) antagonises with one lower end of the lactic acid and thus retards the biotic production of lactic acid by *Lactobacillus pentosus* SH-114.

There is limited specific published data directly addressing the influence of the NSAID flurbiprofen on metabolic pathways governing lactic acid formation in *Lactobacillus pentosus* SH-114. However, general studies indicate that some NSAIDs, including flurbiprofen, can inhibit the growth of lactobacilli, which may indirectly affect metabolic activities like lactic acid production. Lactic acid formation in *Lactobacillus pentosus* generally involves enzymes such as lactate dehydrogenase that convert pyruvate into lactic acid through pathways including the Embden-Meyerhof-Parnas and phosphoketolase pathways for hexoses and pentoses metabolism, respectively.

Lactobacillus pentosus metabolizes sugars via specific pathways that lead to lactic acid production, and lactic acid bacteria's enzyme systems are key to this process. Flurbiprofen and other NSAIDs have been found to inhibit the growth of *Lactobacillus species*, which might alter the enzymatic activity or the bacteria's metabolic capacity to produce lactic acid but detailed mechanistic studies on flurbiprofen specifically affecting these pathways in *L. pentosus* SH-114 are not readily available in the literature.

More broadly, NSAIDs can influence gut microbiota and inflammatory pathways, which can have secondary effects on bacterial metabolism, including lactic acid production. For example, some *Lactobacillus strains* are reported to exert protective roles against NSAID-induced intestinal damage, potentially linked with their lactic acid production and modulation of inflammatory signaling.

In summary, while flurbiprofen may inhibit growth of *Lactobacillus species*, thereby potentially impacting lactic acid metabolic pathways in *Lactobacillus pentosus* SH-114, detailed experimental results specifically showing its influence on metabolic pathways of lactic acid formation are not explicitly documented in accessible research sources.

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