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Cariogenic potential analysis among commonly used paediatric liquid medicaments: An *in vitro* study

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Abstract:
Paediatric liquid medicaments may increase childhood caries risk because of their sugar content and viscosity. Therefore, it is of interest to evaluate the eight commonly prescribed paediatric liquid medicaments for pH, viscosity, sugar content and *Streptococcus mutans* inhibition. Significant differences were observed among formulations ($p < 0.001$), with six showing high sucrose, high viscosity and no antibacterial activity. Only antibiotic suspensions inhibited *S. mutans*, whereas most non-antibiotic formulations exhibited a high cariogenic profile. These findings identify sucrose and viscosity as key determinants of cariogenic potential and support caries-conscious prescribing and sugar-free reformulation.

Keywords: Paediatric liquid medicaments, dental caries, sucrose content, viscosity, pH, *Streptococcus mutans*, *in vitro* study

Background:
Dental caries remains one of the most frequent chronic diseases of childhood and continues to present a significant burden on oral health, quality of life and healthcare systems worldwide. The disease is multifactorial, but the presence of fermentable dietary sugars in the oral environment is a key modifiable driver of demineralisation. Systematic reviews of human studies have confirmed a consistent positive association between the amount of free sugars consumed and caries experience across age groups and support recommendations that limiting free sugar intake to below approximately 10% of total energy reduces caries risk **[1].** In children, both cross-sectional and longitudinal data suggest that greater free-sugar exposure is associated with higher prevalence and severity of caries, even after adjustment for socio-demographic and behavioural covariates **[2].** The cariogenic effect of sugars is mediated not only by total intake but also by their physical form, retention in the mouth, frequency and timing of consumption and relationship to oral biofilm. Liquid, sugar containing preparations that are slowly cleared from the mouth, consumed in small and frequent amounts, or taken at bedtime when salivary flow rate is low are especially dangerous because they extend the period during which plaque pH remains below the critical threshold for enamel demineralisation **[3, 4].** Beyond foods and drinks, paediatric formulations of medications represent another, often overlooked, source of fermentable carbohydrates and acids in the daily exposure profile of young children **[5, 6].** Liquid medicaments are broadly prescribed in children for various acute and chronic conditions, including respiratory infections, asthma, epilepsy, haematological disorders and nutritional deficiencies. To ensure palatability and therapeutic compliance, these products routinely include sucrose, glucose, fructose or other caloric sweeteners alongside acidulates, flavouring agents and viscosity enhancing vehicles **[7].** Commercial paediatric formulations have been reported to exhibit a high prevalence of endogenous pH at or below the critical pH for hydroxyapatite dissolution, moderate-to-high titratable acidity, appreciable fermentable sugar concentrations and relatively high viscosity that may extend oral clearance time **[8]**. Children undergoing long-term treatment could therefore be exposed to repeated, potentially sustained acid and sugar challenges to the dentition in the absence of immediate tooth-brushing following medicine administration **[9]**. A growing body of *in vitro* and *in vivo* research has examined the dental effects of pediatric liquid medicaments. Clinical and epidemiological studies have shown that children exposed to chronic use of sugar-containing or acidic medicines show higher caries experience and, in some cases, greater prevalence of dental erosion compared with unexposed peers, suggesting that these products can act as co-factors in disease rather than therapeutically neutral agents **[10].** *In vitro* investigations have characterised the physicochemical profiles of different therapeutic classes including antibiotics, antitussives, anticonvulsants, antipyretics and vitamin supplements-documenting wide variability in pH, titratable acidity, total soluble solids and sugar content and identifying subsets of formulations with especially unfavourable combinations of low pH, high acidity and high sugar concentration **[11].** Other experimental work has demonstrated that many commonly used pediatric liquid medicaments are capable of lowering plaque pH and enhancing *Streptococcus mutans* growth, reducing enamel microhardness and increasing surface roughness, further reinforcing their potential to contribute to both cariogenic and erosive processes when used frequently or over prolonged periods **[12].** However, the cariogenic potential of pediatric liquid medicaments available in different markets is not uniform and newer or commonly prescribed products may not have been comprehensively evaluated with respect to the key determinants of cariogenicity. Existing studies also vary in design, sample selection and outcome measures and many focuses on limited therapeutic categories or products that may not reflect contemporary prescribing patterns **[13].** Therefore, it is of interest to evaluate the selected pediatric liquid medicaments by determining their endogenous pH, fermentable sugar content and viscosity and by assessing their influence on *S.mutans* growth, with the purpose of generating comparative data that can inform more caries-conscious prescribing and parental counselling in pediatric dental practice.

Materials and Methods:
Study design:
The cariogenic potential of eight commonly prescribed pediatric liquid medicaments (PLMs) was studied *in vitro* by analysis of

endogenous pH and viscosity, fermentable sugar content and their influence on the growth of *Streptococcus mutans*.

Selection of pediatric liquid medicaments:
Eight PLMs were selected on the basis of their widespread use in pediatric clinical practice for children aged 0–12 years and their ready availability as oral liquid formulations in local pharmacies.

Inclusion criteria:
[1] Pediatric liquid medicaments commonly prescribed for children in the age group 0–12 years.
[2] Liquid oral formulations (syrups, suspensions).
[3] Commercially available products that was sealed, labelled and available in pharmacies, with routine use in pediatric practice.

Exclusion criteria:
[1] Expired, unlabelled, unsealed or damaged products.
[2] Non-standardised herbal or alternative medicines.
[3] Solid dosage forms, including tablets, capsules or dispersible tablets.

Test materials:
The following eight pediatric liquid medicaments were included and coded for analysis. All samples were used as supplied by manufacturers, without dilution and stored and handled according to label recommendations until testing:
[1] A – Ibugesic Plus (antipyretic/analgesic)
[2] B – Crocin (antipyretic)
[3] C – Moxikind-CV (antibiotic)
[4] D – Azee (antibiotic)
[5] E – Eptoin (anticonvulsant)
[6] F – Valparin (anticonvulsant)
[7] G – A to Z Syrup (multivitamin)
[8] H – Calcimax Plus (calcium supplement)

Measurement of endogenous pH:
The endogenous pH of each medicament was measured using a calibrated digital pH electrode meter. Five millilitres of each liquid medicament was dispensed into a clean glass beaker. The electrode was rinsed with distilled water, gently blotted dry and immersed in the sample. The pH value was recorded after stabilisation of the reading. Measurements were made in triplicate; between samples the electrode was rinsed and re-equilibrated. The mean pH value of each product was used for analysis.

Measurement of viscosity:
Viscosity of each PLM was measured using a laboratory viscometer according to the manufacturer's operating instructions. Approximately 250 mL of each medicament was placed in the viscometer cup. Viscosity in mPa·s (cP) was recorded at a constant temperature and spindle speed standardised for all samples. Three consecutive readings were obtained and the mean value taken as the representative viscosity.

Estimation of sugar content:
High-performance liquid chromatography (HPLC) was used to estimate the fermentable sugar content of the selected medicaments. A 5 mL aliquot of each medicament was prepared for injection by dilution where required and filtered through a suitable membrane filter to remove particulate matter. Aliquots were injected into the HPLC system under standardised operating conditions and concentrations of glucose and sucrose were quantified by reference to calibration curves constructed from known standards. Sugar content was expressed as percentage concentration per unit volume.

Microbiological testing of *streptococcus mutans* growth:
The ditch plate method was used to study the effect of each PLM on the growth of *Streptococcus mutans*. Sterile agar plates were pre-inoculated with a standardised suspension of *S. mutans* to form a confluent bacterial lawn. Longitudinal ditches were made into the agar surface and defined volumes of each medicament introduced into separate ditches. Plates were incubated at 37°C in a humid incubator under appropriate atmospheric conditions for the required period. After incubation, bacterial growth around each ditch was evaluated visually and compared between medicaments. All observations were recorded in a standardised manner for subsequent analysis.

Evaluation of cariogenic potential:
For each medicament, the measured endogenous pH, viscosity, sugar content and microbiological findings were considered together as integrated indicators of cariogenic potential. Products with lower pH values, higher viscosities, higher fermentable sugar content and greater *S. mutans* growth were interpreted as having higher cariogenic potential relative to other products.

Data handling and statistical analysis:
All numerical data from pH, viscosity and sugar content measurements were entered into a spreadsheet. For each medicament, mean and standard deviation (SD) were calculated from triplicate measurements. Intergroup comparisons were performed using one-way ANOVA at a significance level of $p < 0.05$. Tukey post-hoc tests were applied to identify pairwise differences among products.

Results:
A to Z Syrup, Calcimax Plus, Crocin, Ibugesic Plus, Eptoin and Valparin exhibited no zone of inhibition (mean = 0.00 ± 0.00 mm), indicating a complete absence of antibacterial activity under the experimental conditions. In contrast, Moxikind CV demonstrated the highest mean zone of inhibition (41.33 ± 2.31 mm), followed by Azee (21.33 ± 1.15 mm). One-way ANOVA revealed a statistically significant overall difference ($F = 860.229$; $p < 0.001$). Post hoc Tukey comparisons confirmed that Moxikind CV had a significantly greater zone of inhibition compared with all other formulations ($p < 0.001$), followed by Azee, which also differed significantly from all others ($p < 0.001$). No statistically significant differences were observed

among the six non-antibiotic formulations (p = 1.000) **(Table 1).** Mean pH values ranged from 6.13 ± 0.15 (A to Z Syrup) to 7.77 ± 0.21 (Calcimax Plus), indicating variability in acidity and alkalinity among the preparations. One-way ANOVA revealed a statistically significant overall difference (F = 28.585; p < 0.001). Detailed pairwise comparisons demonstrated the following: A to Z Syrup (pH 6.13) differed significantly from Ibugesic Plus (p = 0.002), Moxikind CV (p = 0.001) and Azee (p < 0.001), but not from Crocin (p = 0.679), Eptoin (p = 0.796) or Valparin (p = 0.323), all of which clustered in the near-acidic range. Calcimax Plus (pH 7.77) showed significant differences from Crocin (p < 0.001), Ibugesic Plus (p = 0.001), Eptoin (p < 0.001), Valparin (p < 0.001) and Moxikind CV (p = 0.004), but not from Azee (p = 0.796), indicating both were near-neutral to slightly alkaline. Crocin (pH 6.40) differed significantly from Azee (p < 0.001) and Moxikind CV (p = 0.015), but not from A to Z Syrup, Eptoin or Valparin (p > 0.05). Ibugesic Plus (pH 6.93) was significantly more alkaline than A to Z Syrup (p = 0.002) and Crocin (p = 0.035), but did not differ from Eptoin (p = 0.166) or Moxikind CV (p = 0.997); it was significantly more acidic than Azee (p = 0.023). Eptoin (pH 6.37) did not differ significantly from A to Z Syrup, Crocin or Valparin, but differed significantly from Moxikind CV (p = 0.053) and Azee (p < 0.001). Valparin (pH 6.50) was significantly more acidic than Moxikind CV (p = 0.010) and Azee (p < 0.001) but comparable to A to Z Syrup, Crocin and Eptoin (p > 0.05). Moxikind CV (pH 7.03) differed significantly from A to Z Syrup, Crocin, Eptoin and Valparin (p < 0.05), but not from Ibugesic Plus (p = 0.997) or Azee (p = 0.079), indicating these three formulations were close to neutral **(Table 2).** All pediatric medicaments were markedly more viscous than water (0.890 cP). Calcimax Plus exhibited the highest viscosity (32.36 cP), followed by Crocin 120 (30.88 cP) and A to Z Syrup (30.11 cP). Eptoin (26.82 cP) and Azee XL (26.36 cP) demonstrated intermediate values, while Ibugesic Plus measured 23.46 cP. The dry syrup (Moxikind CV reconstituted) recorded 14.90 cP and Valprol (Valparin oral solution) showed the lowest viscosity at 2.90 cP **(Table 3).** Sucrose was detected at high concentrations in most formulations. Ibugesic Plus recorded the highest sucrose content (94.06%), followed by Eptoin (87.09%), Crocin (79.8%), Azee (78.7%) and Calcimax (73.7%). Valparin (50.8%) and A to Z Syrup (49.6%) contained moderate sucrose concentrations. Glucose was quantifiable only in Eptoin (3.2%) and A to Z Syrup (18.8%). Sugar values were not reportable for Moxikind CV under the applied analytical conditions **(Table 4).**

Table 1: Comparison of zone of inhibition for eight different formulations

Group	Mean (mm)	SD	F-value	p-value
A to Z Syrup	0.00	0.00	860.229	< 0.001*
Calcimax Plus	0.00	0.00		
Crocin	0.00	0.00		
Ibugesic Plus	0.00	0.00		
Eptoin	0.00	0.00		
Valparin	0.00	0.00		
Moxikind CV	41.33	2.31		
Azee	21.33	1.15		

*One-way ANOVA with Tukey post hoc test; * significant at p ≤ 0.05*

Table 2: Comparison of pH for eight different formulations

Group	Mean pH	SD	F-value	p-value
A to Z Syrup	6.13	0.15	28.585	< 0.001*
Calcimax Plus	7.77	0.21		
Crocin	6.40	0.20		
Ibugesic Plus	6.93	0.21		
Eptoin	6.37	0.12		
Valparin	6.50	0.10		
Moxikind CV	7.03	0.15		
Azee	7.53	0.31		

*One-way ANOVA with Tukey post hoc test; * significant at p ≤ 0.05*

Table 3: Measurement of viscosity of samples

Sr. No.	Sample Name	Density (g/mL)	Viscosity (cP)
1	Water	0.997	0.890
2	Valprol	1.121	2.90
3	Eptoin	1.241	26.82
4	A to Z	1.309	30.11
5	Crocin 120	1.303	30.88
6	Azee XL	1.241	26.36
7	Ibugesic Plus	1.227	23.46
8	Calcimax	1.301	32.36
9	Dry Syrup	0.972	14.90

Table 4: Measurement of sugar content of pediatric syrups

Sr. No.	Name of Syrup	% Glucose	% Sucrose
1	Ibugesic Plus	NA	94.06
2	Crocin	NA	79.8
3	Moxikind CV	NA	NA
4	Azee	NA	78.7
5	Eptoin	3.2	87.09
6	Valparin (Sodium Valproate Oral Solution)	NA	50.8
7	A to Z Syrup	18.8	49.6
8	Calcimax	NA	73.7

NA = not available/not detected under the applied analytical conditions

Discussion:

The findings of the present study characterised the physicochemical and microbiological profiles of eight commonly prescribed pediatric liquid medicaments and showed that anticaries considerations had not been prioritised to the same extent as palatability and pharmacological efficacy in the design of these formulations. The combination of mildly acidic pH, high sucrose concentrations and elevated viscosity indicated that many non-antibiotic preparations were capable of adhering to tooth surfaces, exhibiting slow oral clearance and supplying fermentable substrate to cariogenic biofilms for extended periods. The absence of detectable antibacterial activity against *S. mutans* in six of eight formulations further indicated that these products would not counteract their own cariogenic potential through any intrinsic antimicrobial mechanism. In contrast, the antibiotic suspensions demonstrated strong inhibition of *S. mutans* growth, although their sugar and viscosity profiles did not systematically correlate with a low-cariogenic profile. The pH range recorded in the present study (6.13–7.77) was higher than that reported in numerous previous surveys of pediatric liquid medicaments, where the majority of formulations exhibited pH values below the critical threshold of 5.5 for enamel dissolution **[14].** Researchers recorded pH ranges of approximately 4.2-6.1 for various frequently prescribed pediatric liquids, in which all products were rated as inherently acidic and cariogenic **[15].** In contrast, the syrups analysed in the present study were closer to neutrality; however, the statistically

significant intergroup differences ($F = 28.585$; $p < 0.001$) confirmed that meaningful variation existed within this apparently narrow range and mildly acidic values around pH 6 may still support demineralising conditions in plaque when combined with high sugar availability and limited salivary clearance. Sucrose was present at high concentrations in most of the medicaments tested, reaching above 90% in Ibugesic Plus and remaining above 70% in several others, while glucose was detected in only two products. This pattern is consistent with broader market surveys showing that the vast majority of pediatric liquid medicines contain sucrose as their principal sweetener **[16].** Researchers also reported that over three quarters of children's syrups in their setting contained high soluble sugar content and exhibited considerable erosive potential, they also found that both medicines and vitamin or mineral supplements often combined sucrose and acidic components to produce high total soluble solids and titratable acidity **[17].** Although the viscosity values recorded were lower than the extreme viscosities reported for some antiepileptic formulations reaching several hundred cP in certain published series they remained sufficiently elevated to suggest slow clearance from tooth surfaces, consistent with other analyses of pediatric medicines **[18].** Studies combining viscosity measurements with enamel softening tests showed that higher viscosity, especially when associated with sucrose-rich vehicles, extended the residence time of solutions in fissures and interdental areas, prolonging acid production and mineral loss **[19].** The viscosity profile obtained in the present study therefore supported the interpretation that, even without strongly acidic pH, repeated exposure to these syrups could contribute to a significant cariogenic challenge. In the present panel, Eptoin and Valparin had only mildly acidic pH values but showed high sucrose content and viscosities in the mid-20 cP range, indicating that antiepileptic syrups may remain cariogenic even after pH-oriented reformulation, consistent with previous studies reporting low pH, high titratable acidity and marked enamel softening for several antiepileptic liquids **[20].** A similar pattern was observed for multivitamin and mineral preparations: A to Z Syrup and Calcimax combined high viscosity and sucrose content despite pH values closer to neutrality, matching the profile documented in previous work showing erosive effects on primary enamel for such preparations **[21].** The microbiological results clearly separated antibiotic from non-antibiotic formulations. Six non-antibiotic preparations produced no inhibition zone against *S. mutans*, indicating neither inhibition of bacterial growth nor any offset of their sugar-induced cariogenicity, consistent with previous reports that most non-antibiotic pediatric syrups do not inhibit *S. mutans* **[22].** The two antibiotic suspensions yielded clear inhibition zones, corroborating studies indicating that certain liquid antibiotics reduce *S. mutans* growth and biofilm formation**;** however, other investigations have showed that antibiotic syrups with antimicrobial properties may still exhibit acidic pH, high sugar content and detectable erosive potential **[21]** and the present findings confirmed a similar mixed-risk profile. Broader evidence from *in vitro* and clinical research indicates that pH, titratable acidity, sugar concentration and viscosity, together with the pattern of exposure, collectively determine the cariogenic and erosive impact of pediatric liquid medications **[23].** Large surveys from multiple settings report that many children's medicines display at least one unfavourable physicochemical characteristic, while a substantial proportion combines several such factors. Recent work using profilometer and scanning electron microscopy showed clear enamel surface loss and microstructural changes after repeated exposure to certain syrups in scenarios mimicking long-term therapy **[23],** while a narrative synthesis concluded that high sugar content, low pH and high viscosity consistently increase caries and erosion risk in chronically medicated children **[24].**

Conclusion:

Most pediatric liquid medicaments exhibited cariogenic properties, including high sucrose content and elevated viscosity, while only two demonstrated significant antibacterial activity. Repeated administration of sugar-rich formulations may increase caries risk, emphasizing the need for caries-conscious prescribing. Oral hygiene counselling and sugar-free, low-viscosity formulations may help minimize medication-associated caries in children.

Limitations:

This study had certain limitations. The *in vitro* design did not reproduce the complex intraoral environment, including salivary flow, pellicle formation, dietary interactions and patient-specific oral hygiene behaviours; therefore the measured parameters could only approximate *in vivo* cariogenicity. Analysis was restricted to eight formulations from a single market and to single batches of each product, limiting generalisability across brands, countries and production lots. Sugar content could not be quantified for all medicaments and only sucrose and glucose were assessed, leaving other fermentable carbohydrates uncharacterised.

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Data availability: The datasets generated and analysed during the current study are available from the corresponding author on reasonable request

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