



INTERNATIONAL JOURNAL OF ADVANCE RESEARCH, IDEAS AND INNOVATIONS IN TECHNOLOGY

ISSN: 2454-132X

Impact Factor: 6.078

(Volume 7, Issue 4 - V7I4-1695)

Available online at: <https://www.ijariit.com>

Longevity of the antimicrobial effect of Silver Diamond Fluoride on cariogenic bacteria in children- A Systematic review

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ABSTRACT

Aim: To critically evaluate the effect of Silver diamine fluoride (SDF) on the bacterial load of cariogenic bacteria in children. Electronic databases were searched from Google Scholar, PubMed, Wiley online library, SciELO, Science Direct, Scopus, Cochrane from 2013 till 15th of August 2020 to list out studies undertaken to evaluate the effect of silver diamine fluoride on cariogenic bacteria in children from 2 to 10 years. Abstracts and subsequently eligible full-text articles were screened. **Results:** Six hundred sixty-five studies were obtained from all the databases. After a thorough screening, five studies met all the inclusion criteria. Four studies assessed the bacterial load with the microbiological culture method, two studies assessed bacteria with Adenosine triphosphate (ATP) bio-luminometer. **Conclusion:** Peak antimicrobial action of SDF was appreciated from the 3rd -30th day of post-application.

Keywords: "Silver diamine fluoride" cariogenic bacteria, diammine silver fluoride cariogenic bacteria, diamine silver fluoride cariogenic bacteria.

1. QUESTION

After the application of SDF does a bacterial load of cariogenic bacteria changes?

2. INTRODUCTION

Dental caries is a universal disease that affects people regardless of age, gender, socioeconomic status. It is biofilm-mediated, diet modulated, multifactorial, non-communicable, a dynamic disease resulting in net mineral loss of dental hard tissues [Fejerskov 1997; Pitts et al., 2017]. It is determined by biological, behavioral, psychosocial, and environmental factors. As a consequence of this process, a carious lesion develops [1]. Caries is the most common childhood illness, that occurs five times more often than the second most common childhood illness, asthma [2]. Both Miller's concept and Keyes triad stated that two major components play a vital role in the caries process which are microorganisms and fermentable substances. Fermentable substances have various factors to be taken into consideration like the frequency of intake, a form of intake and chemical formula of substances but in microorganisms, mostly *Streptococcus mutans* initiates the process of dental caries which is further progressed with the help of *Lactobacillus* species and are so-called cariogenic bacteria [3].

The clinical and radiographic examination of caries is not sufficient for proper diagnosis and treatment of children with high caries risk. Caries activity tests provides a better understanding and proper guidance for the management of caries in individuals who are more prone to caries and are classified as high-risk patients. Bacterial culture is one of the most reliable methods used for accurate measurement of bacterial load, which is more technique sensitive because of difficulty in collecting samples and transporting to selective medium. Apart from bacterial culture, there are numerous other tests like Cariostat, Caries detecting dyes, and Cariscreen which helps in evaluating the total bacterial load in the oral cavity but not specific bacteria. There is an association between high levels of microorganisms present in the saliva of patients with a high risk of carious disease [3]. This leads to a need for specific

preventive measures, which provides both long term antimicrobial effect and remineralization characteristics. Silver diamine fluoride (SDF) is one of the material that has both the re-mineralizing and antimicrobial action which is used in Minimally invasive dentistry (MID) to preserve the tooth structure.

SDF was first recorded to be used in Japan in the early 1970s, which is a transparent, odorless solution comprising of silver, fluoride complexed with ammonia. Ammonia is the stabilizer that is used to maintain the constant concentration of solution over a long period. Another product named Advantage Arrest (Elevate Oral Care, Florida), not available in the UK, is tinted blue. Concentration of fluoride present in SDF (38%) around 44,800 ppm and one drop (0.05ml) contains only 2.24 mg of fluoride. SDF has various modes of chemical reaction with carious tooth tissue forming calcium fluoride and silver phosphate which reduces tooth sensitivity and carious lesion by blocking the dentinal tubules. SDF also causes bacterial death, remineralization of the demineralized teeth structure, and inhibition of dentinal collagen degradation. SDF has a bactericidal effect on micro-organisms which eventually disrupts the dental plaque biofilm. Silver ions in SDF interact with proteins and deoxyribonucleic acid (DNA) of bacteria and inhibit cell wall synthesis.

The demineralized tooth surfaces treated with SDF have significantly less growth of cariogenic species compared to non-SDF treated surfaces. The results from previous studies concluded that there was remineralization of demineralized inorganic tooth mineral by fluoride ions and the resultant fluorapatite causes the tooth more resistant to acid dissolution. Food and Drug Administration (FDA) in the United States cleared SDF in 2014, to treat dentine hypersensitivity [4].

SDF is available in different concentrations from 12-38%, Fung MHT (2018) conducted a randomized clinical study to compare the effectiveness of 12 and 38% of SDF applied semi-annually or annually in arresting active caries in primary teeth and finally revealed that 38% is more effective than 12% regardless of their variation in the frequency of application [5].

An unesthetic disadvantage of SDF is the black staining of the arrested carious lesion of teeth. An effective method to overcome this drawback is to apply a saturated solution of potassium iodide (KI) immediately after the SDF application which results in the formation of Silver iodide, white precipitate that masks the staining. This reaction doesn't alter caries arresting effect of SDF, the bond strength of GIC to dentine, and did not adversely interfere with the fluoride uptake into the adjacent demineralized dentine [6,7]. A novel product Riva Star whose pH value is 13, consists of both SDF and KI which is available in two bottles or two capsule systems [8]. There are reviews evaluating the caries preventing and promotion of remineralization of SDF in both children and adults but no review on the longevity of antimicrobial action of SDF over the bacterial load in the oral cavity.

The objective of this review is an attempt to critically evaluate the longevity of the bactericidal effect of SDF on cariogenic bacteria in the oral cavity at different time intervals.

3. METHODS

3.1 Type of studies, participants, and intervention

- a. Randomized controlled and clinical studies where caries activity test is done with a sample size of $n \geq 20$.
- b. Age- 2-10-year-old children.
- c. Bacterial load after application of SDF at different time intervals.

3.2 Search strategy:

Two trainees performed an electronic search in English language from seven databases (Google Scholar, PubMed, Science Direct, Scopus, SciELO, Cochrane, Wiley Online Library) at time period from January 2013 to 15th August 2020. The search strategy focused on one aspect:

The Longevity of the antimicrobial effect of SDF after application.

Keywords like "Silver diamine fluoride" cariogenic bacteria and diamine silver fluoride cariogenic bacteria, diamine silver fluoride cariogenic bacteria are searched. The procedures involved in collecting the records and evaluating them are represented in figure 1. All the studies with the above keywords are collected from seven databases. Duplicate studies are removed and initially in vitro, and ex vivo studies are excluded which is subsequently followed by exclusion of 2 in vivo studies with sample size <20. These studies don't mimic the bacterial load and salivary clearance which plays a vital role in caries development and progression in the oral environment.

To complete the search, references of each selected publication about bacterial load after SDF application in different time intervals are also searched based on the inclusion and exclusion criteria enlisted in table 1.

The titles and abstracts which did not present enough relevant information, are obtained in full text format to critically appraise the studies on bacterial load of cariogenic bacteria after SDF application at different time intervals. Both the investigators collected the studies from seven databases individually and then the results were compared. To identify the inter-rater reliability in the selection of studies Cohen's kappa statistics was done and the value of kappa is 0.68. There was no disputes or disagreement on the selection of study.

4. RESULTS

The electronic database and number of studies screened and selected are depicted in Table 2. The search revealed 552 studies published in Google Scholar, 9 in PubMed, 2 in Cochrane, 76 in Science Direct, and 26 in Wiley Online Library. All the five studies that met the inclusion criteria had a common database Google scholar. The level of evidence of this systematic review is

moderate, because of less number of studies, small sample size, short duration of the study, lack of definitive evaluating method and lack of control group in one study. Further studies should be conducted and documented on the bacterial load after SDF application in children at a different time interval to frame a new protocol.

This review was an initiative to recommend further microbiological studies that are technique sensitive but paves way for the definitive conclusion on the action of SDF over the cariogenic bacterial load at different time intervals. A summary of sample size, caries risk tests used, and methodology of the SDF application is presented in Table 3.

Evaluation of selected studies:

a Microbiological culture tests [Shah S et al. (2013) ^[9], Thwin KM (2017) ^[10], Garrostazu MD et al. (2020) ^[11], LaMay A et al. (2020) ^[12]]

b ATP bio-luminometer [Mikati R et al. (2018) ^[13], LaMay A et al. (2020) ^[12]]

5. OUTCOMES OF SELECTED STUDIES

In all the selected five studies, four studies had a single application of 38% SDF within 6-month of time interval except one study ^[12] in which the single and double application of SDF within 6-month time interval was evaluated. There was no beneficial effect on the reduction of *Streptococcus mutans* count but *Lactobacillus* species count was reduced significantly when SDF was applied twice within a 6-month interval. This draws us to the conclusion that semi-annual application of SDF is effective on active caries lesion.

The remaining four studies where SDF was applied once in 6-month were grouped into two different ways to evaluate the bacterial load with time interval after SDF application:

- (a) Baseline to 1 day- 90 day
- (b) Baseline to 6,12,18 months

5.1 Baseline to 1 day-90 day:

Table 4 elaborated on the bacterial load evaluation at baseline to 1 day - 90 days. Two studies ^[9,11] that compared the bacterial load at the above-mentioned interval. In both studies the methods and units used to measure bacterial species were different. *Streptococcus mutans* count reduced significantly in increasing order from SDF, followed by fluoride varnish and APF gel at 72 hours after application while in earlier study *Streptococcus mutans* count after 24 hours and 30 days of application reduced by 95% and 99.95% significantly in both the groups but after 90 days the bacterial count was similar to the colony-forming unit (CFU) obtained after 24 hours of application ^[9].

5.2 Baseline to 6,12,18 months:

Baseline to 6,12, 18-month bacterial load enlisted in table 5. The studies which ^[10,13] evaluated bacterial load at baseline to 6-months found a significant reduction in bacterial load. In a later study, the bacterial load was evaluated with ATP bio-luminometer which reflects overall microbial load and not specifically cariogenic bacteria. Thwin KM ^[13] concluded that bacterial load was significantly changed in the SDF group that was evaluated by Dentocult SM in plaque and cariostat. In both studies, the method used to evaluate the bacterial count is different and so difficult to derive the conclusion.

While the bacterial load was reduced at 6, 12, 18-month when compared to baseline but when it is compared to bacterial load on the 3rd day there is a slight increase ^[9]. This helps us to conclude that the SDF, Fluoride varnish, or gel has its peak antibacterial action on the 3rd day after application which gradually reduced. To maintain uniformity in comparing the antimicrobial effect, all the materials were applied in a similar frequency.

There are no in vivo studies in databases to evaluate the bacterial load from baseline to 1-3 months and to 3-6 months that would help for better assessment of longevity of SDF.

6. COMPARISON OF SDF WITH OTHER CARIOSTATIC AND ANTIMICROBIAL AGENTS

Fluoride is one of the most successful materials preferred in the preventive aspect of dental care. The most frequently used fluoride compound is Sodium fluoride, Acidulated phosphate fluoride, Stannous fluoride. Physicochemical investigation of enamel from deciduous teeth. They concluded that enamel subjected to prenatal fluoridation exhibited changes in crystal structure like an increase in prism dimension causes more homogeneous and denser crystal populations in intra-prismatic regions, greater total mineral density, a higher degree of crystallinity, smaller a-axis dimensions, more fluoride, and fewer carbonate contents ^[14]. However, in vitro studies revealed that the reduction in enamel solubility by pre-eruptive incorporation of fluoride is less and therefore it is unlikely that the fluoride incorporated into enamel plays an important role in the observed caries reduction ^[15,16].

Antimicrobial agent named chlorhexidine is dicationic in nature with pH > 3.5, with two positive charged ions, prevents plaque accumulation and is classified as an antiplaque and anti-gingivitis agent. It is available in concentrations from 0.02-2%, which is bacteriostatic at 0.02-0.06% or bactericidal at 0.2-0.12%. Chlorhexidine binds with hard and soft tissues in the oral cavity and is released slowly with time. Its release depends on various factors such as concentration, pH, temperature, and time of contact of the solution with oral structures. The superior antiplaque effect of Chlorhexidine which makes it gold standard material for its substantivity ^[17].

6.1 SDF with topical fluoride

38% SDF with 6% fluoride varnish (Bifluorid) and 1.23% APF → SDF provided superior antimicrobial effect than Fluoride varnish and APF gel which are recommended by American Dental Association (ADA) for semi-annual or annual application in preventing caries in the primary and permanent dentition of children and adolescents ^[9].

The effectiveness of 38% SDF on oral microbial load was in comparison to 5% sodium fluoride varnish (gold standard treatment) in pediatric patients with extensive caries^[13]. The bacterial load assessed with ATP bioluminescence and results revealed that there was a significant difference in the SDF group ($p=0.01$) than the fluoride varnish group.

The above fact was contradicted by 38 %SDF was comparable to 5% sodium fluoride and effective in arresting carious lesions and diminishes the number of cariogenic bacteria present in plaque and degree of acid production^[10].

6.2 SDF with chemical plaque controlling agent

Antimicrobial effect of 30% SDF with 1% chlorhexidine → After 24 hours and 30 days of application *Streptococcus mutans* reduced significantly but after 90 days the bacterial count increased which was similar to CFU obtained after 24 hours of application. The effectiveness of reducing *Streptococcus mutans* is similar for both groups but SDF had an advantage over CHX because it causes hardening of dental structures, hindering biofilm adherence^[11].

An in vivo and in vitro study in children, comparing the antimicrobial effect of SDF, SDF+ KI, CHX (positive control), and Saline (negative control). In vitro part of the study reported that zone of inhibition was in increasing order from SDF alone (25.7mm), CHX (23.03mm), SDF + KI (15.15mm) and the saline group did not show any reduction of bacteria while in vivo part revealed that SDF, SDF+KI resulted in > 90% of reduction of anaerobes and 100% reduction of total viable bacteria in MSR agar^[18].

SDF is preferred as an effective preventive measure in reducing and arresting dental caries in primary teeth. A study on the root or cervical caries lesion of adults resulted in a hardening of 60% of the carious lesion^[19]. An in vitro study reported that after application of 38% SDF on carious lesion reported in the formation of filamentous densities or microwires associated with the hardening of the lesion. They concluded that SDF achieves its antimicrobial functions by biochemical interactions and through its ability to penetrate into dentin^[20]. A remarkable finding from in vitro studies on the penetration of SDF reported the extend of microwires 700 μm pulpally into lesions as compared to studies which reported the extending of microwires around 200–300 μm into dentin^[21]. Recently, other in vitro study reported silver microwires comprising of silver and chloride in the ratio of 3:1 had a length of 50 to 2100 μm and a diameter of 0.25 to 7 μm in dentinal tubules which increases the hardness and stiffness of dentin^[22]. SDF not only hardens the carious lesion but also prevents collagen degradation of dentin by enzyme collagenase. The inhibitory effect of different concentrations of SDF like 38%, 30%, and 12% on Cathepsin, matrix metalloproteinases (MMPs) showed that 38% SDF had the greatest inhibitory effects on cathepsin B, K and MMP-2, MMP-8, and MMP-9^[23,24]. A significant reduction of *Streptococcus mutans* count in dentinal tubules after SDF treatment^[25]. An in vivo study on 14 subjects resulted that there was no change in the total bacterial count but caries-related species were reduced in arrested caries while increased in active caries^[26].

7. LIMITATIONS OF THIS REVIEW

The primary drawback was the lack of many clinical studies on the bactericidal effect of SDF. There were numerous in vitro studies that were excluded because they don't mimic the natural environment of the oral cavity which always undergo numerous changes in pH, flow, nature of saliva during function, parafunctional movements. The saliva obtained for microbiological study in four studies while in one study Dentocult SM strip was used. There was a wide variation in the method of salivary collection, in three studies stimulated saliva was collected after 1-2 minutes but in one study unstimulated saliva was collected. A dramatic 3-fold increase in bacterial diversity in stimulated salivary samples. A possible reason can be the removal of bacterial biofilms attached to different surfaces of the oral cavity, especially the tongue during chewing of paraffin gum^[27]. *Streptococcus mutans*, pioneer bacteria in the initiation of caries is dominant in unstimulated saliva. The age group of the children taken in 3 studies was ≥ 5 who are advised to brush under proper supervision but in two studies 2-6 years-old children who need to be brushed by the parent or caretaker. The amount of toothpaste used by these children is also different^[28]. Lastly, the concentration of SDF used was not constant which might alter the antimicrobial action.

8. CONCLUSION

From the above reviewed studies following conclusions are obtained:

- (a) Peak antimicrobial action of SDF was appreciated from the 3rd -30th day of post-application.
- (b) SDF has antimicrobial action and substantivity similar to Chlorhexidine.

Further numerous studies are recommended to evaluate the bacterial load after SDF application in a different time interval which will be helpful to formulate a new guideline on the frequency of SDF application.

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APPENDIX

Table 1: Inclusion and exclusion criteria are listed based on which studies are screened and selected.

Inclusion criteria	Exclusion criteria
Randomised Controlled and Clinical studies	Review, case reports
Studies in which Caries activity test done	Sample size <20
Sample size > 20	Other language
Children from 2-10 years	In vitro, ex vivo studies
Studies in English language	

Table 2: Number of studies obtained from each database and studies that are selected for review

Databases	No. of studies obtained	No. of studies screened	No. of studies selected
Google scholar	552	37	5
PubMED	9	4	-
Science Direct	76	2	-
Wiley online library	26	-	-
Cochrane	2	-	-
Scopus	-	-	-
SciELO	-	-	-

Table 3: Summary of selected studies sample size, caries activity test implemented and methodology of SDF use.

Author	Sample size	Control group	Experimental group	Caries risk test implemented	Application of SDF
Shah et al. (2013) ^[9]	n=123 (8 year- old children)	Fluoride varnish (Bifluorid12), APF gel	38% SDF	Tryptone- yeast- cysteine sucrose bacitracin agar (TYCSB) media	Single application of SDF on posterior teeth for 3-4 minutes with microbrush
Thwin KM (2017) ^[10]	n=201 (3-4 year-old children)	Sodium fluoride varnish	38% SDF followed by Sodium fluoride varnish	Dentocult SM and Caristat	Single application of SDF for 3 minutes followed by NaF varnish application at every 6 months
Mikati R (2018) ^[13]	n=50 (2-6 year-old children)	5% NaF varnish	38% SDF	ATP bioluminescence	SDF applied for 3 minutes at every 6 months interval.
Garrastazu MD et al. (2020) ^[11]	n=90 (6-10 year-old children)	1% chlorhexidine gel	30% SDF	Mitis salivarius agar plate culture	Single application for 3 minutes
La May et al. (2020) ^[12]	n=40 (2-6 year-old children)		SDF applied only once at 6-month, SDF applied twice first at 3 month and second at 6 month.	Brain heart infusion agar, Mitis Salivarius bacitracin agar, Rogosa agar plate culture.	SDF applied for 3 minutes

Table 4: Bacterial load from baseline to 1 day-3 months

Author, time interval	Control group (Baseline)	Control group (different time interval)	Experimental group (Baseline)	Experimental group (different time interval)
Shah S et al. (2013) ^[9] 72 hours after application	6% fluoride varnish: 8.7×10 ³ CFU/ml APF gel: 8.6×10 ³ CFU/ml	6% fluoride varnish: 3.8×10 ³ CFU/ml APF gel: 6.9×10 ³ CFU/ml	38% SDF: 20.3×10 ³ CFU/ml	5.3×10 ³ CFU/ml
Garrastazu MD et al. (2020) ^[11]	1% CHX: 6.35E+07 +2.28E+08 ^{Aa}	24 hours→ 4.16E+06± 6.60E+06 ^{Ba} 30 days→ 3.07E+04 ± 2.86E+04 ^{Ca} 90 days→ 2.92E+06 ± 3.48E+06 ^{Ba}	30% SDF: 8.79E+07 ± 4.62E+08 ^{Aa}	24 hours→ 3.92E+06 ± 5.92E+06 ^{Ba} 30 days→ 3.06E+04 ± 3.09E+04 ^{Ca} 90 days→ 2.94E+06 ± 5.97E+06 ^{Ba}

Table 5: Bacterial load from baseline to 6,12,18 months

Author	Control group (Baseline)	Control group	Experiment group (Baseline)	Experiment group
Shah S et al. (2013) ^[9] 6 month	6% Fluoride varnish: 8.7×10 ³ CFU/ml APF gel: 8.6×10 ³ CFU/ml	6% Fluoride varnish: 6-month: 5.9×10 ³ CFU/ml 12-month: 6.7×10 ³ CFU/ml 18-month: 6.1×10 ³ CFU/ml APF gel: 6-month: 7.4×10 ³ CFU/ml 12-month: 8.3×10 ³ CFU/ml 18-month: 7.4×10 ³ CFU/ml	38% SDF: 20.3×10 ³ CFU/ml	38% SDF: 6-month: 5.3×10 ³ CFU/ml 12-month: 6.5×10 ³ CFU/ml 18-month: 5.3×10 ³ CFU/ml
Thwin KM (2017) ^[10]	5% Sodium fluoride Dentocult SM plaque: 0.72+0.66	Dentocult SM plaque: 0.71+0.63 Dentocult SM tongue:	38% SDF Dentocult SM plaque: 0.95+0.70	Dentocult SM plaque: 0.56+0.51* Dentocult SM tongue:

	Dentocult SM Tongue: 0.60+0.78 Cariostat: 1.39+0.57	0.60+0.78 Cariostat: 1.46+0.57	Dentocult SM tongue: 0.76+0.80 Cariostat: 1.61+0.81	0.62+0.57 Cariostat: 1.37+0.52*
Mikati R (2018) ^[13]	ATP Bioluminescence 5% NaF: 7756-9746 RLU	2221-9907RLU	38% SDF: 6327-9862RLU	2780-8927RLU

RLU- Relative light unit, * statistically significant (p<0.001)

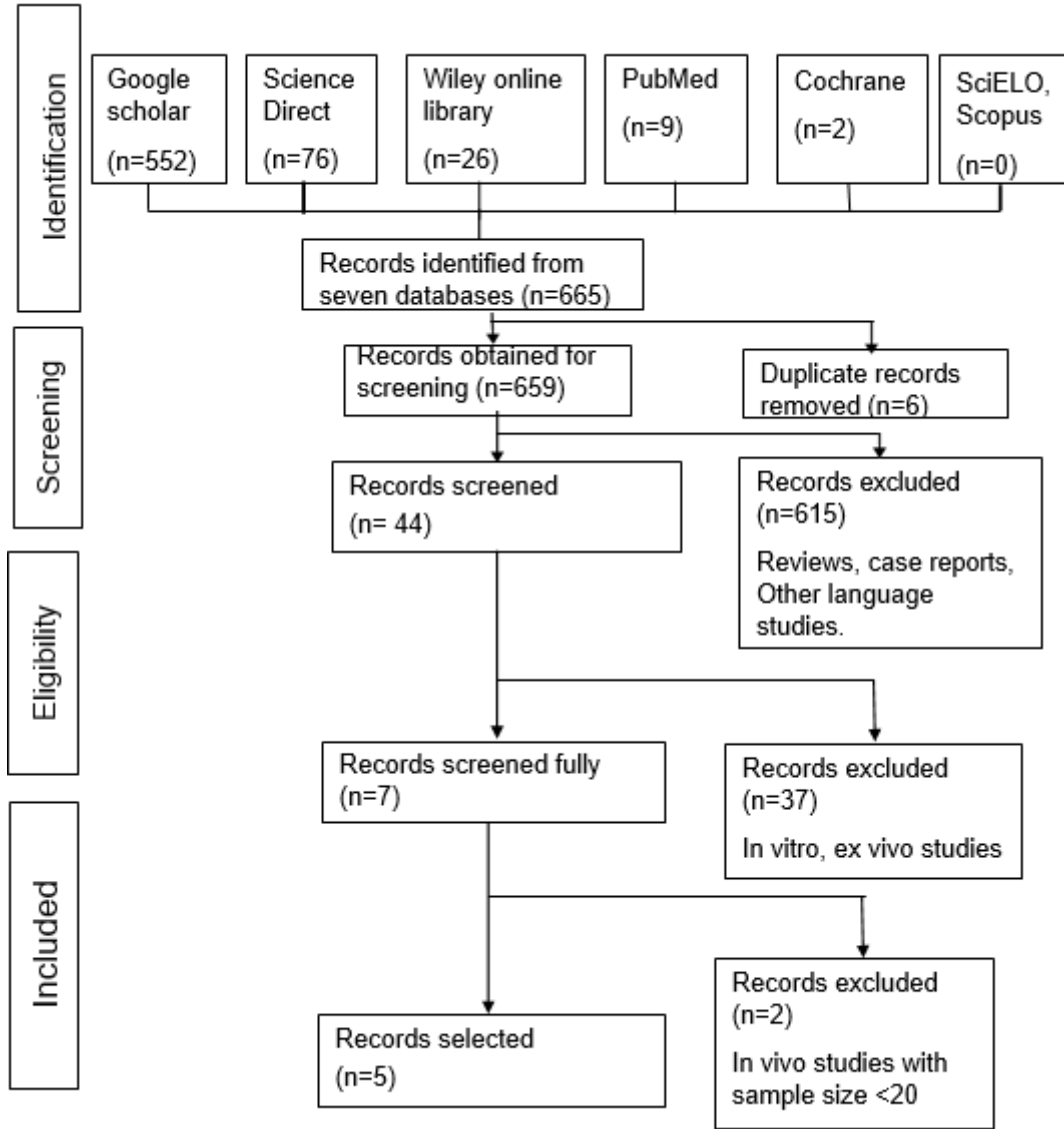


Figure 1: Flowchart of the procedure used to obtain the records for review.