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Original Article

Safety and Efficacy of Sodium Alginate and Mesna in Endoscopic Submucosal Dissection: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Sodium hyaluronate, commonly used in ESD, has drawbacks such as high cost and potential tumorigenesis. Sodium alginate (Na alginate) and Mesna offer promising alternative solutions with their viscoelastic and mucolytic properties. In this review, we aimed to evaluate the safety and efficacy of Na alginate and Mesna solutions in ESD.
Methods: A systematic search was conducted across multiple databases. Inclusion criteria were randomized controlled trials and observational studies assessing Na alginate and Mesna in ESD. The primary outcome included en bloc resection rates. Secondary outcomes included adverse events such as perforation and delayed bleeding, and procedural time.
Results: Eight studies involving 255 patients were included in this analysis. Overall en-bloc resection rate for sodium alginate was 97% [95% CI (93%-99%); I2: 0%]. En-bloc resection subgroup analysis revealed 97% [95% CI (93%-99%); I2: 0%] for 0.6% sodium alginate and 95% [95% CI (70%-99%); I2: 0%] for 0.4% sodium alginate. Moreover, the en-bloc resection rate for Mesna was 98% [95%CI (92%-100%); I2: 0%]. Delayed bleeding rates for sodium alginate were 5% [95% CI (1%-20%); I2: 65.2%]; however, after subgroup analysis delayed bleeding was 2% [95% CI (1%-6%); I2: 0%] for 0.6% sodium alginate and 22% [95% CI (8%-49%); I2: 0%] for 0.4% sodium alginate. Perforation rate for 0.6% sodium alginate was 1% [95% CI (0%-5%); I2: 0%].
Conclusion: Na alginate (0.6%) and Mesna are effective and safe alternatives to sodium hyaluronate for submucosal injection in ESD. These solutions offer potential cost-effective and safer options for clinical practice, with Na alginate (0.6%) showing particularly low rates of adverse events.

1. Introduction

The burden of gastrointestinal tumors is rapidly increasing worldwide and is associated with significant morbidity and mortality. Colorectal cancer ranks third in incidence and second in mortality worldwide, with esophageal cancer ranking as the eighth most diagnosed cancer [1, 2]. Endoscopic submucosal dissection (ESD) has gained increasing acceptance as a suitable approach for gastrointestinal cancers due to its low rate of local recurrence compared to endoscopic mucosal resection [3, 4, 5].

The submucosal injection is a critical step in ESD, as it forms a submucosal cushion fluid that facilitates the elevation and separation of the lesion from the muscularis propria. This enhances en bloc resection and decreases the risk of complications by creating a physical barrier protecting deep tissues [6, 7, 8]. The ideal submucosal injection solution should fulfill the following criteria: (1) Ensure an adequately thick submucosal fluid cushion; (2) it should be capable of long-term retention under the mucosa, minimizing the need for frequent submucosal injections; (3) It should be affordable, readily accessible, simple to store, and administer; (4) Minimizing the occurrence of adverse events during ESD, such as hemorrhage and perforation, and maintaining the integrity of excised specimens to ensure accurate pathological results [6]. Currently, sodium hyaluronate is one of the most common solutions used for ESD. However, it has been confirmed that it may stimulate tumor growth after ESD [9].

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Mensa is a thiol compound commonly used as prophylaxis against some chemotherapy drugs to prevent hemorrhagic cystitis. Additionally, Mensa exhibits a mucolytic effect, which is utilized to facilitate sputum expectoration during respiratory distress. Due to its unique chemical property, Mesna can break down disulfide bonds that connect polypeptide chains, which soften connective tissue fibers between different anatomical planes. Several clinical surgical studies have shown that applying an aqueous solution of Mesna directly to the surgical area helped in smoother blunt dissection and led to shorter operation times, decreasing the risk of hemorrhage [10, 11, 12, 13, 14].

Na alginate (SA) has excellent water retention and viscoelastic properties. It is used in clinical settings to treat peptic ulcers or as a hemostatic agent [15, 16, 17]. SA has been used in Japan for more than 60 years as a protective agent for the digestive mucosa, typically at a 5% concentration. This extensive use has established the efficacy and safety of SA [18]. In 2018, Japan approved 0.6% SA for use as a submucosal injection solution in ESD [19]. We conducted this meta-analysis to evaluate the feasibility and safety of Na alginate and Mesna before endoscopic submucosal dissection.

2. Methods

2.1. Search Strategy and Data Extraction

A systematic search of relevant literature was conducted across multiple databases, including Embase, Scopus, Web of Science, Medline/PubMed, and Cochrane, from their inception to April 17, 2034. The search strategy utilized Boolean operators to combine terms related to "endoscopic submucosal dissection" or "submucosal dissection" or "ESD" AND "Mesna" AND "Na alginate". The search aimed to identify studies investigating the efficacy and safety of those two solutions for submucosal injection during endoscopic submucosal dissection (ESD) in patients with gastrointestinal adenomas and early-stage neoplastic lesions eligible for ESD treatment. Two independent reviewers screened titles, abstracts, and full-text articles for inclusion based on predefined eligibility criteria. Any discrepancies were resolved through discussion or consultation with a third reviewer. Data extraction was conducted independently by two co-authors using a standardized form, with discrepancies resolved through consensus. Our research adhered to the recommended guidelines for reporting systematic reviews and meta-analyses. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed to ensure transparency and completeness in reporting. Furthermore, we conducted systematic reviews and meta-analyses following the Cochrane criteria and the PRISMA checklist [20, 21]

2.2. Inclusion Criteria and Study Outcomes

Studies eligible for inclusion in this systematic review and meta-analysis were randomized controlled trials (RCTs) and observational studies focusing on patients with gastrointestinal adenomas and early-stage neoplastic lesions eligible for ESD treatment. The intervention of interest was the use of Mesna or Na alginate for submucosal injection during ESD procedures. Comparisons with other solutions were not applicable in this case. The primary outcomes of interest included procedural time, while secondary outcomes included en bloc complete dissection rate, amount of solution injected, and adverse events associated with those submucosal injection solutions. Procedural time refers to the duration of the ESD procedure. En bloc complete dissection rate indicates the proportion of cases where the lesion was completely removed in one piece. Adverse events encompass any undesirable effects related to the use of submucosal injection solutions, which include perforation, intra-operative bleeding, and post-operative delayed bleeding, which is defined as any bleeding after the patient leaves the operating room till one month later. Exclusion criteria comprised studies not written in English or with inadequate translation, case reports, editorials, letters, or conference abstracts without full-text availability, animal studies, or studies conducted on non-human subjects. Additionally, studies involving patients with contraindications or specific conditions that could significantly impact outcomes were excluded.

2.3. Risk of Bias Assessment

Two authors independently assessed the risk of bias and methodological quality of included studies. The Cochrane risk-of-bias tool for randomized trials (ROB 2) was used for RCTs, while for non-randomized clinical trials, the ROBINS-I tool was employed [22, 23]. Any discrepancies are resolved through discussion or consultation with a third reviewer.

2.4. Statistical Analysis

The forest plots illustrate the rates (shown by the black square) and 95% confidence interval (CI) shown by a horizontal line from non-comparative studies. The area of the black square is proportional to the specific study weight in the overall meta-analysis. The overall pool is visible in the middle of the red diamond shape representing the overall rate, and its width indicates the pooled 95% CI. For comparative studies, proportional variables were analyzed and mean differences (MD) with the corresponding 95% CI. All analyses were performed using Comprehensive Meta-analysis software [24].

3. Results

3.1. Study and patient characteristics

We ran a systematic search in our databases and identified 1130 studies, of which eight studies were included in our analysis [25, 26, 27, 28, 29, 30, 31, 19]. Detailed information about the selection of studies is shown in the PRISMA flow diagram **(Figure 1)**. A total of 415 patients were included in our analysis. 63% were men and 37% were women. The mean age ranged from 53 to 69 years **(Table 1)**.

3.2. Quality of included studies

Quality assessment of our included studies was assessed using the Cochrane RoB 2 tool for four RCTs. Two studies had a total low risk of bias status, and the other two had a Moderate risk of bias status. Non-randomized studies were assessed using the ROBINS-I tool. The four studies had a moderate risk of bias **(Table 2)**.

3.3. En-bloc resection

Five studies were pooled to evaluate the rates of en-bloc resection using 0.4% and 0.6% Na alginate, with an overall rate of 97% [95% CI (93%-99%); I2: 0%] **(Figure 2)**. Subgroup analysis with three studies pooled for the rates of en-bloc resection using Na alginate 0.6% with an overall rate of 97% [95% CI (93%-99%); I2: 0%] **(Figure 3)**. Two studies were pooled for the rates of en-bloc resection using Na alginate 0.6% with an overall rate of 95% [95% CI (70%-99%); I2: 0%] **(Figure 4)**. Three studies were pooled to evaluate the rates of en-bloc resection using Mesna with an overall rate of 98% [95% CI (92%-100%); I2: 0%] **(Figure 5)**.

3.4. Perforation, delayed bleeding, and procedural time

Two studies were pooled for the rates of Perforation for 0.6% Na Alginate with an overall rate of 1% [95% CI (0%-5%); I2: 0%] **(Supplementary figure 1)**. Five studies were pooled for the rates of

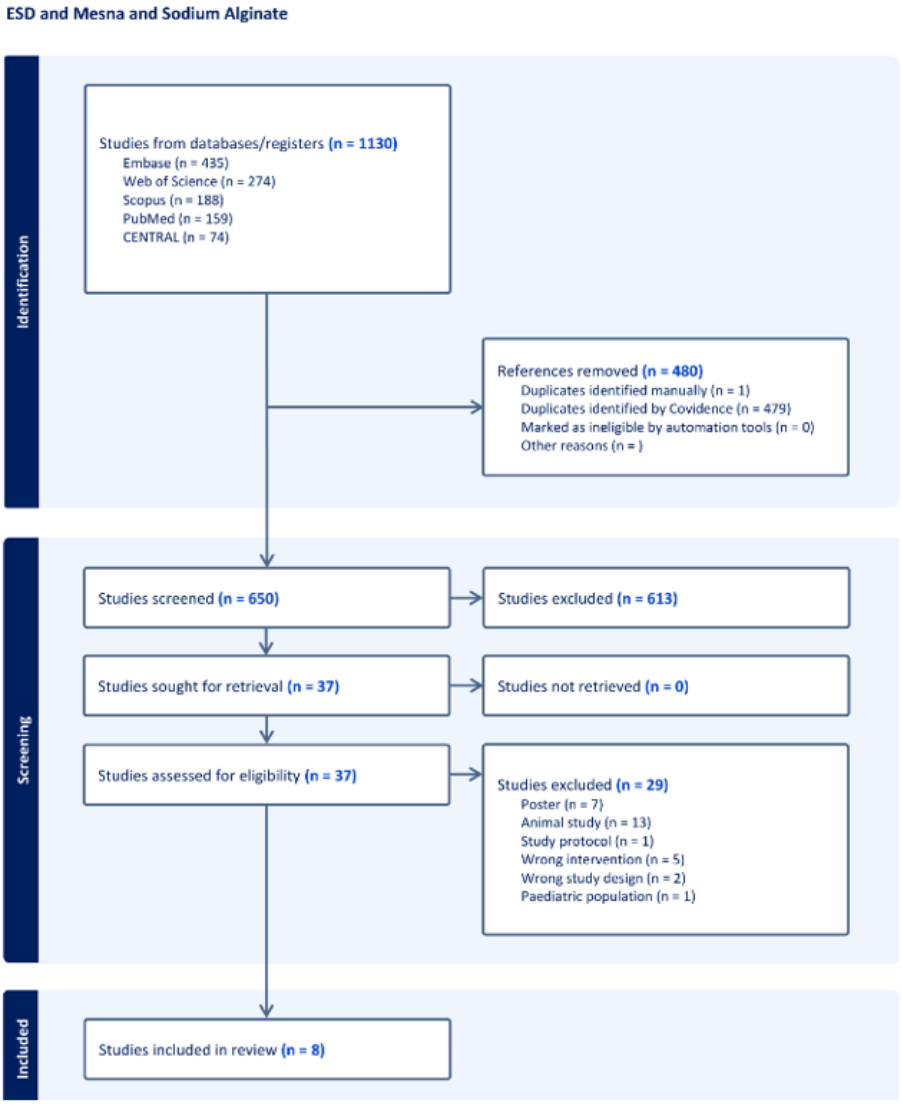

Figure 1: PRISMA flow chart diagram for our literature review results.

Delayed bleeding using Na alginate 0.6% and 0.4% with an overall rate of 5% [95% CI (1%-20%); I2: 65.21%] **(Supplementary figure 2)**. Three studies were pooled for the rates of Delayed bleeding using 0.6% Na alginate, with an overall rate of 2% [95% CI (1%-6%); I2: 0%] **(Supplementary Figure 3)**. Two studies were pooled for the rates of Delayed bleeding using Na alginate 0.4% with an overall rate of 22% [95% CI (8%-49%); I2: 0%] **(Supplementary figure 4)**.

Five studies were pooled to evaluate the mean Procedure time in minutes using Na alginate 0.4% and 0.6% [(Mean 60.86, 95% CI: 45.06 to 76.67); I2: 85.8%] **(Supplementary figure 5)**. Three studies were pooled to evaluate the mean Procedure time in minutes using Na alginate 0.6% [(Mean = 45.77, 95% CI: 32.94 to 58.59); I2: 80.7%] (Supplementary figure 6). Two studies were pooled to evaluate the mean Procedure time in minutes using Na alginate 0.4% [(Mean = 85.38, 95% CI: 61.29 to 109.47); I2: 24.8%] **(Supplementary figure 7)**. Three studies were pooled to evaluate the mean Procedure time in minutes using Mesna [(Mean = 28.54, 95% CI: 13.39 to 43.71); I2: 96.39%] **(Supplementary figure 8)**. The pooled results from two studies comparing Mesna and normal saline reporting the procedure time showed no significant difference between the two groups, [(MD: -6.55, 95% CI: -13.42 to 0.33; P=0.06); I2: 0%], as shown in **(Supplementary figure 9)**

4. Discussion

The high cost and potential tumorigenesis associated with sodium hyaluronate (SH) [25, 9], a widely used ESD submucosal injection solution, prompted the search for an alternative. In the early 2010s, Akagi et al. proposed Sodium alginate (SA) as a safe and effective submucosal injection solution. SA is a non-toxic natural polysaccharide polymer isolated from brown seaweed [25]. In addition to its low cost, SA is known for its safety, having been used in the treatment of peptic ulcer disease due to its protective and hemostatic properties on the mucosal membrane [15]. Lastly, the viscosity of SA helps in achieving reliable submucosal lift [9]. An early clinical experience with 3% SA in ESD was reported on 11 patients with early gastric cancer. The overall endoscopic en bloc resection rate was 100%. No major complications occurred with no tumor recurrence after a mean follow-up of 28 months [25].

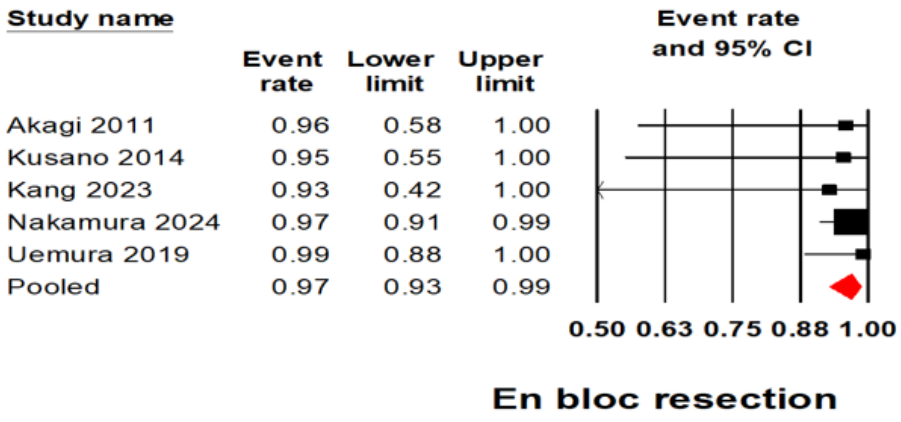

Figure 2: En-bloc resection rate (both 0.4% and 0.6% Na Alginate).

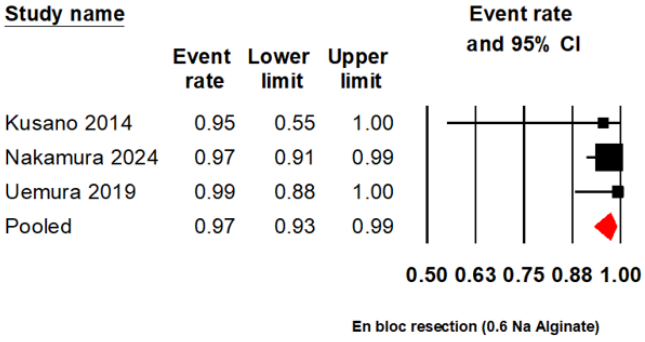

Figure 3: En-bloc resection (0.6% Na Alginate).

Later, the formulation of SA was improved to 0.6% to enhance injectability and facilitate uniform mucosal elevation [28].

A randomized controlled trial (RCT) compared the efficacy and safety of 0.6% SA to 0.4% SH in ESD for esophageal and gastric lesions. Efficacy was based on the en bloc complete resection rate in ESD and the formation and maintenance of mucosal elevation upon injection. SA was found to be non-inferior to SH. In addition, the mucosal resection time was similar between the two groups [19].

Table 1: Characteristics of included studies

Author	Country	Study design	Total participants (n)	ESD group Gender (female) N (%)	Used solution	Procedure location	Size of lesion (Mean ± SD), mm
Akagi, 2011 [25]	Japan	Clinical trial	11	2 (18)	0.4% Sodium alginate	Stomach	15.5±5.3
Kusano, 2014 [28]	Japan	Clinical trial	10	2 (20)	0.6% Sodium alginate	Stomach	16.21±5.8
Kang, 2023 [27]	Taiwan	RCT	12	8 (66)	0.4% Sodium alginate	Stomach, colon & esophagus	30.0±5.5
Nakamura, 2024 [29]	Japan	Cohort	100	40 (40)	0.6% Sodium alginate	Rectum and colon	20.89±8.8
Uemura, 2019 [19]	Japan	RCT	122	13 (21.7)	0.6% Sodium alginate	Stomach and esophagus	NA
Dobashi, 2015 [26]	Japan	RCT	40	1 (5)	Mesna	Esophagus	23.33±9.9
Sumiyama, 2010 [30]	Japan	Prospective cohort	20	NA	Mesna	Stomach	21.7±12.14
Sumiyama, 2014 [31]	Japan	RCT	100	9 (18)	Mesna	Stomach	19.49±11.74

RCT, Randomized Controlled Trial; ESD, Endoscopic Submucosal Dissection; SD, Standard Deviation; NA, Not Available; mm, Millimeter.

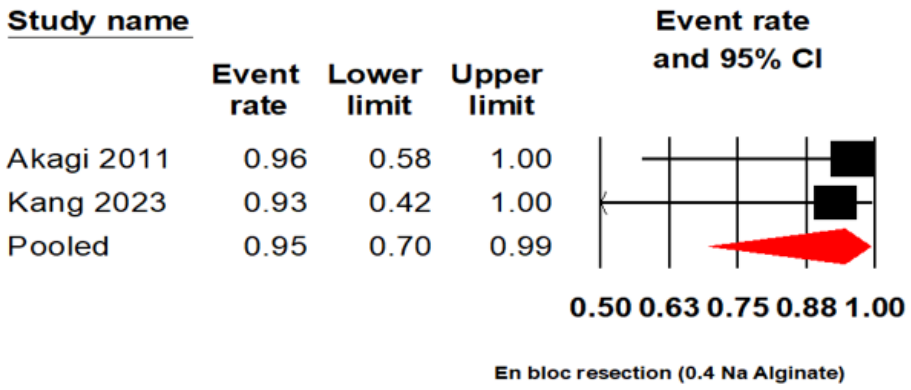

Figure 4: En-bloc resection (0.4% Na Alginate).

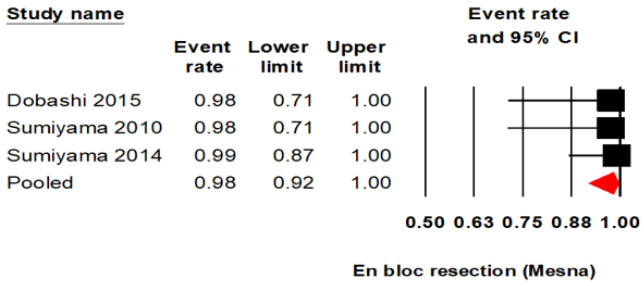

Figure 5: En-bloc resection (Mesna).

Table 2: Risk of bias assessment for included studies

Author name, year	Study design	Tool used	Overall ROB
Akagi, 2011 [25]	Clinical trial	ROBINS-I	Moderate
Kusano, 2014 [28]	Clinical trial	ROBINS-I	Moderate
Kang, 2023 [27]	RCT	Cochrane RoB 2	Low
Nakamura, 2024 [29]	Cohort	ROBINS-I	Moderate
Uemura, 2019 [19]	RCT	Cochrane RoB 2	Moderate
Dobashi, 2015 [26]	RCT	Cochrane RoB 2	Moderate
Sumiyama, 2010 [30]	Prospective cohort	ROBINS-I	Moderate
Sumiyama, 2014 [31]	RCT	Cochrane RoB 2	Low

RCT, Randomized Controlled Trial; ROB, Risk of Bias.

The primary utility of Mesna is to facilitate submucosal dissection by dissolving disulfide bonds, thereby softening the connective tissue fibers [30]. This also allows for less or no electrosurgical dissection, theoretically reducing the risk of perforation. In a pilot study, chemically assisted ESD with submucosal injection of Mesna led to a 100% en-bloc resection rate with a mean operation time of 21.17 ± 11.6 minutes [30]. Subsequently, a double-blind RCT comparing Mesna to saline submucosal injection in ESD for gastric cancer found no difference in submucosal dissection time between the two groups [31]. However, there were fewer time-consuming cases (more than 30 minutes) in the Mesna group (P=0.049). Additionally, the subjective difficulty of ESD was significantly lower in the Mesna group. Both groups had similar en-bloc resection rates (Mesna: 100%, Controls: 98.08%) and perforation rates (Mesna: 0%, Controls: 1.92%) [31].

As for the adverse events, we found that, in the aspect of perforation incidence, Na alginate was slightly safer than the standard used solution, sodium hyaluronate (1% in the Na alginate cases vs. 3% in the sodium hyaluronate in previous trials) [32]. When we compared the incidence of delayed bleeding between sodium hyaluronate and Na alginate solutions, it was found that Na alginate (with a pooled incidence of 5% for both 0.4% and 0.6% concentrations) is not as safe as sodium hyaluronate (with a pooled incidence of 1%). However, if we compare the two concentrations of Na alginate, the concentration of (0.6% Na Alginate) is much safer than (0.4% Na Alginate) (adverse event rates are 2% and 22%, respectively). This detail should guide future studies to focus more on the safer (0.6%) concentration in trials, maximizing the benefits of the new solution while minimizing the risk of adverse events. Our study has some limitations. First, it includes a small number of single-arm studies without comparative ones. Additionally, there are some variations in results during subgroup analysis. This persistent heterogeneity is likely attributable to differences in endoscopist skill levels and procedural efficiency across centers rather than the intervention itself. Variations in technique, experience, and procedural protocols

at different institutions inherently contribute to the observed discrepancies in procedure duration, making it a challenging factor to standardize across studies. Finally, all the studies are conducted in Asia with small sample sizes, which may limit the generalizability of our results. We suggest conducting randomized controlled trials to guide future directions, choices, and careful interpretation of results. Future enhancements should prioritize expanding network diversity, improving data validation mechanisms, and developing more sophisticated tools for bias mitigation.

5. Conclusion

Our study revealed that both Na alginate, especially Na alginate (0.6%), and Mesna are effective and safe alternatives to sodium hyaluronate for submucosal injection in endoscopic submucosal dissection. Na alginate (0.6%) achieved high en-bloc resection rates with notably low adverse event rates, making it a particularly promising option. Mesna also showed excellent en bloc resection rates and significantly reduced procedural times, highlighting its efficiency in ESD procedures. Both solutions offer cost-effective and safer options for clinical practice, addressing the limitations associated with sodium hyaluronate, such as high cost and potential tumorigenic risk. Future studies should focus on further validating these findings through larger randomized controlled trials and exploring the optimal concentrations and formulations for enhanced safety and efficacy.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Institutional Review Board (IRB)

None

Large-Language Model

None

Authors' Contribution

HA conceptualized the study; HA and AA developed the methodology; HA and IST conducted literature search; IAR and MAE performed screening; HA, IST, and IAR handled data extraction; MAMA and MAE validated the data; IST, AYA, and OA assessed risk of bias; AA conducted statistical analysis; MAMA provided statistical review; AA created data visualizations; HA and AA wrote the manuscript; AA, AYA, and MN reviewed and edited; AA, AJA, and SA supervised the project. All authors reviewed and approved the final manuscript.

Data Availability

This review article does not contain any new primary data. All information discussed is derived from previously published sources and publicly available databases, as cited in the manuscript.

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