# Unveiling the Influence of Osmotic Pretreatment on Dried Fruit Characteristics: A Meta-Analysis Approach

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**ABSTRACT:** Considering the diverse findings regarding the impact of osmotic pretreatment on the quality of dried products, it is important to determine whether osmotic pretreatment can either maintain or reduce the quality of fruit products. Thus, the present study aimed to scrutinize research regarding the influence of osmotic pretreatment on the qualities of dried fruits through meta-analysis. The Scopus database was used to search for relevant articles. Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocol, 26 studies that met the criteria for meta-analysis were identified. The presentation included statistics (mean, standard deviation, sample size) and moderator variables (fruit types, osmotic agents, solution concentrations, drying methods, and drying temperatures). After pooling data using a random effects model, the OpenMEE software was used to conduct meta-analysis. The results showed that osmo-dried fruits had significantly decreased total color difference, titratable acidity, total flavonoid content, and vitamins B<sub>1</sub> and B<sub>3</sub> (*P*<0.05) and significantly increased β-carotene and 2,2-diphenyl-1-picrylhydrazyl levels (*P*<0.05). Osmotic pretreatment did not affect total phenolic content and vitamin C. Subgroup analysis highlighted the influence of moderator variables on the quality of osmo-dried fruits, with each fruit responding differently to osmotic pretreatment. Moreover, using 10% sugar solution as an additive effectively enhanced the quality of dried fruits. In addition, osmotic dehydration can be combined with convective drying at a temperature of 60°C for optimal results in the drying process.

Keywords: color, flavonoids, food preservation, vitamins

### **INTRODUCTION**

Fruits are agricultural commodities with significant moisture content, making them vulnerable to spoilage. To address this issue, drying has been widely used to decrease moisture content and water activity (Onwude et al., 2017). However, drying may compromise the quality of the final product. Fortunately, several pretreatment methods (both thermal and nonthermal) have been developed to minimize quality degradation during the drying process (Pu and Sun, 2017; Deng et al., 2019; Bassey et al., 2021).

Osmotic pretreatment is one nonthermal pretreatment (NTP) method that can preserve quality; it applies osmotic pressure to a high-concentration solution to force water molecules out of the cellular particles of materials with high moisture content (Pravitha et al., 2021). The osmotic solution usually comprises sugar, organic acid, and sodium chloride (Lewicki, 1998). NTP applications, including osmotic pretreatment, can prevent the negative effects of heat on nutritional value, color, and flavor of dried agricultural products (Osae et al., 2020). According to a previous study, osmotic pretreatment decreased nutrition loss and enzymatic browning processes (Ahmed et al., 2016). This finding was also corroborated by Pandiselvam et al. (2022) who concluded that the advanced osmotic pretreatment method inhibits phytochemical, flavor, color, and aroma degradation.

However, several studies found that osmotic pretreatment decreases the quality of dried products. One study found that chokeberry juice and a mixture of chokeberry juice and sucrose subjected to osmotic pretreatment exhibited a higher total color change value than samples

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without pretreatment (Kowalska et al., 2020). In other studies, sweet cherry and raspberry subjected to osmotic pretreatment exhibited lower total phenolic content (TPC) than non-pretreated samples (Franceschinis et al., 2015; Sette et al., 2017). In addition, osmotic pretreatment greatly decreased vitamin C levels in pequi and pineapple (de Mendonça et al., 2017; Zzaman et al., 2021).

Because of these diverse findings, it is important to determine whether osmotic pretreatment can preserve or decrease the quality of dried products. To verify this, a meta-analysis, which synthesizes findings from multiple independent studies to determine the overall significance of the treatment impact on the control group, can be utilized (Červenka et al., 2018). The primary conclusion regarding the significance of the treatment effect on the control can be reached by analyzing the outcomes of multiple studies and calculating their effect sizes (Borenstein et al., 2009).

Recently, several studies have investigated the effects of drying on the nutritional content of various foods. Červenka et al. (2018) examined how drying temperature affected ascorbic acid, flavonoid, and phenolic content in food products. They found that the drying temperature had a significant impact on ascorbic acid content but did not affect phenolic and flavonoid content. Kurniasari et al. (2022) investigated the bioactivity of ginger after undergoing different drying methods and found that the phenolic and flavonoid content, 6-gingerol concentration, and antioxidant activity varied depending on the method used. In another study, Yulni et al. (2023) explored the effects of freeze-thaw pretreatment on plant-based food products and found that the TPC and color were decreased, whereas total flavonoid content (TFC) was increased. In light of these studies, our research focuses on the impact of osmotic pretreatment on the qualities of dried fruit. This study aimed to examine the effects of osmotic pretreatment before drying on the qualities of dried fruit [color, vitamin B<sub>1</sub>, vitamin B<sub>3</sub>, vitamin C, titratable acidity (TA), total flavonoid,  $\beta$ -carotene, 2,2-diphenyl-1-picrylhydrazyl (DPPH), and total phenol] through meta-analysis. The findings are expected to provide a new quantitative reference for the effect of osmotic pretreatment in drying.

### MATERIALS AND METHODS

#### Data source and selection criteria

A literature search was performed using the Scopus database (https://www.scopus.com) in December 2022 to identify relevant studies exploring the impact of osmotic pretreatment on the quality of dried fruit between 2000 and 2022. The search was restricted to peer-reviewed publications in English. The primary search terms that were used included "drying" and "pretreatment" or "pretreatment." Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol (Liberati et al., 2009), a systematic review was conducted to minimize the effects of bias and ensure the quality of the meta-analysis. Several criteria were used for selecting literature based on the PICO protocol (Ogbuewu and Mbajiorgu, 2023): population (referring to dried fruit), intervention (referring to osmotic pretreatment), comparison (referring to osmotic pretreatment), comparison (referring to osmotic pretreatment) and outcomes (referring to total color differences, vitamin B<sub>1</sub>, vitamin B<sub>3</sub>, TA, total flavonoid, total phenolic,  $\beta$ -carotene, and DPPH).

For a comprehensive review, 148 articles that met the criteria were downloaded. However, 122 articles were excluded because of irrelevant quality parameters (42 articles), a lack of conventional osmotic pretreatment (29 articles), and insufficient data for effect size calculations (51 articles). Ultimately, 26 articles were selected after screening and reviewing. These articles were then subjected to data synthesis and statistical analysis. The literature selection procedure based on PRISMA is shown in Fig. 1.

#### Data synthesis

The extracted data included moderator variables and summary statistics. Moderator variables comprised types of fruit, osmotic agents, solution concentrations, drying methods, and drying temperatures. In terms of summary statistics, the mean values, standard deviation, and sample size for control and treatment samples were included. To ensure consistency, the measurement units for each quality parameter that was examined were homogenized. WebPlotDigitizer (https://apps.automeris.io/wpd/) was used to extract data from histograms and graphs, facilitating accurate retrieval and utilization of information.

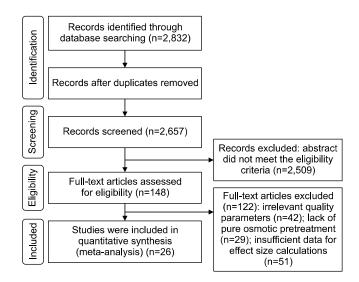


Fig. 1. Flow chart of the search results and selection details based on PRISMA.

### Statistical analysis

In the meta-analysis, standardized mean differences with 95% confidence intervals (95% CIs) were used to assess the effect size based on the mean difference between dried fruits without pretreatment (control) and those subjected to osmotic pretreatment. This method was selected because of its ability to calculate the effect size while excluding sample measurement units, variance, sample size, and statistical test results (Sánchez-Meca and Marín-Martínez, 2010).

Subgroups of various moderator variables, including types of fruit, osmotic agent, solution concentration, drying method, and drying temperature, were analyzed to determine the cumulative effect size (Table 1). This approach aimed to discern the effects of these variables on the magnitude of the impact of osmotic pretreatment on outcome measurement. Subgroups with fewer than three comparisons were excluded from the meta-analysis (Ogbuewu and Mbajiorgu, 2023). The sources of heterogeneity were evaluated using Q and inconsistency index  $(I^2)$  statistics (Higgins and Thompson, 2002). A pooled estimate was deemed significant when the 95% CI did not encompass zero. All calculations were performed using the OpenMEE Software (Wallace et al., 2017).

## **RESULTS AND DISCUSSION**

### Overview of studies included in the meta-analysis

Osmotic pretreatment was employed during the drying process to maintain the quality of the dried product (Sereno et al., 2001). Numerous studies have explored the effects of osmotic pretreatment (Tortoe, 2010; Yadav and Singh, 2014; Chandra and Kumari, 2015; Ahmed et al., 2016; Landim et al., 2016; Shete et al., 2018; Osae et al., 2020; Pandiselvam et al., 2022). However, to the best of our knowledge, this study is the first to apply meta-analysis approaches in assessing the impact of osmotic pretreatment on the quality of dried fruits. The literature search on the Scopus database yielded 2,832 potential

Table 1. Results of data extraction utilized in the meta-analysis

Reference	Fr	ruit	Osmotic agent	Concentration (%)	Drying method	Temperature (°C)	Quality
Prothon et al. (2001)	Subtropical	Apple	S	50 <sup>s</sup>	М	50, 60, 70	1
Kowalski and Mierzwa (2013)		Apple	S	40 <sup>5</sup>	С	55	1
Xiao et al. (2018)		Apple	S	40 <sup>s</sup>	ICPD	90, 95, 70	1, 4
Wang et al. (2019)		Apple	S	60 <sup>s</sup>	MV	50	1, 2, 4, 7
Önal et al. (2019)		Apple	S, St	1.8 <sup>s</sup> , 0.1 <sup>st</sup>	С	50, 55, 60, 65	1
Cichowska-Bogusz et al. (2020)		Apple	S, SA	30 <sup>SA</sup> , 50 <sup>S</sup>	C, MV, C-MV	70	1
Feng et al. (2022)		Apricot	S	30 <sup>s</sup> , 45 <sup>s</sup> , 60 <sup>s</sup>	С	60	4, 7
Andreou et al. (2021)		Fig	S, A, St	80 <sup>s</sup> , 1.5 <sup>A</sup> , 1 <sup>st</sup>	С	50, 60, 70	7
Lyu et al. (2017)		Kiwi	S	70 <sup>s</sup>	IR	50, 60, 70	1
Mannozzi et al. (2020)		Kiwi	S	40 <sup>s</sup>	С	50, 60, 70	4, 7
Xu et al. (2020)		Kiwi	S	30 <sup>s</sup> , 45 <sup>s</sup> , 60 <sup>s</sup>	С	60	1
Tylewicz et al. (2022)		Kiwi	S	40 <sup>S</sup>	С	50, 60, 70	1
An et al. (2018)		Plum	S	60 <sup>s</sup>	С	60	4
Paraskevopoulou et al. (2022)		Pumpkin	SA, S, A, St	40 <sup>SA</sup> , 20 <sup>S</sup> , 2 <sup>A</sup> , 3.5 <sup>St</sup>	С	60	7
Kowalska et al. (2020)		Quince	S, FJ	65.1 <sup>FJ</sup> , 70 <sup>S</sup> , 70.3 <sup>FJ</sup>	C, MV, F	60, -40	1
Macedo et al. (2021)		Strawberry	S	35 <sup>s</sup>	С	60	1, 4, 9
Chua et al. (2004)	Tropical	Banana	S	15 <sup>s</sup> , 25 <sup>s</sup> , 35 <sup>s</sup>	С	40	1
Rai et al. (2022)		Banana	S	35 <sup>s</sup> , 50 <sup>s</sup> , 65 <sup>s</sup>	С	60, 65, 70	1, 4
Özkan-Karabacak et al. (2022)		Citrus	S	45 <sup>s</sup>	V	70	4
Roy et al. (2022)		Citrus	S, St	10 <sup>s</sup> , 2 <sup>st</sup>	С	45, 50, 55	1, 3, 4, 5, 6, 7, 9
Kek et al. (2013)		Guava	S	35 <sup>s</sup> , 70 <sup>s</sup>	С	70	7
Zou et al. (2013)		Mango	S	65 <sup>S</sup>	C-EP	50	1, 2
Udomkun et al. (2018)		Papaya	S	30 <sup>s</sup>	F	-25	1, 4, 8
Chandra et al. (2021)		Papaya	S	25 <sup>s</sup>	С	60	1, 4
Zzaman et al. (2021)		Pineapple	S, St	1 <sup>s</sup> , 2 <sup>st</sup> , 10 <sup>s</sup>	С	50, 55, 60	1, 2, 3, 4, 5, 6, 7, 8
Hossain et al. (2021)		Taikor	S, St	10 <sup>S</sup> , 20 <sup>S</sup> , 2 <sup>St</sup>	С	45, 50, 55	3, 4, 5, 6, 7, 8, 9

S, sugar; St, salt; SA, sugar alcohol; A, acid; FJ, fruit juice; M, microwave; C, convective; ICPD, instant controlled pressure drop; MV, microwave vacuum; IR, infrared; F, freeze; V, vacuum; C-EP, convective-explosion puffing; 1, total color difference; 2, titratable acidity; 3, total flavonoid content; 4, total phenolic content; 5, vitamin  $B_1$ ; 6, vitamin  $B_3$ ; 7, vitamin C; 8,  $\beta$ -carotene; 9, 2,2-di-phenyl-1-picrylhydrazyl.

references. After applying stringent selection criteria, 26 studies, published between 2001 and 2022, were deemed suitable for inclusion in the meta-analysis. The outcomes of data extraction from the selected studies are presented in Table 1, whereas the pooled results of osmotic pre-treatment and control interventions on the quality of dried fruits are summarized in Table 2.

# Effects of osmotic pretreatment on the quality of dried fruits

As shown in Table 2, osmotic pretreatment significantly affected (P<0.05) various parameters of dried fruits, including total color differences ( $\Delta E$ ), vitamin B<sub>1</sub>, vitamin B<sub>3</sub>, TA, TFC,  $\beta$ -carotene, and DPPH, compared with the control. Conversely, osmotic pretreatment insignificantly affected (P>0.05) TPC and vitamin C.

This study demonstrated that osmotic pretreatment enhanced the color,  $\beta$ -carotene, and DPPH levels of dried fruits compared with untreated samples. This enhancement was attributed to the reduction in the time required for oxidative browning reactions, leading to decreased discoloration (Kowalska et al., 2020). Furthermore, the shorter drying time and formation of new antioxidant compounds contributed to the overall antioxidant activity (Albanese et al., 2013). Additionally, the osmotic solutions created a significant barrier on the cell surface for the release of antioxidant compounds (Nudar et al., 2023) and slowed down  $\beta$ -carotene oxidation (Zzaman et al., 2021).  $\beta$ -Carotene is a constituent soluble in fat (insoluble in water), and its leach during osmotic pretreatment is negligible (de Mendonça et al., 2017).

Osmotic pretreatment was found to cause a reduction in various nutrients in dried fruits, including TFC, TA, vitamin  $B_1$ , and vitamin  $B_3$ . This reduction was attributed to the loss of soluble nutrients during osmotic pretreatment, resulting in a decrease in TFC (Osae et al., 2019). In addition, the sticky syrup produced by the osmotic solution could affect the acidity of the final product and alter its characteristic taste (Tortoe, 2010; Ahmed et al., 2016). Moreover, immersion pretreatments might lead to the leaching of water-soluble vitamins, such as vitamin B, from the product (Hossain et al., 2021).

While osmotic pretreatment was found to have little impact (P>0.05) on the vitamin C levels of dried fruits, it might cause a slight decrease. This phenomenon was likely because of the semipermeable nature of cell membranes during the process, leading to the leaching of minerals, vitamins, and pigments into the osmotic solution (Ciurzyńska et al., 2016). Interestingly, osmotic pretreatment did not significantly affect (P>0.05) TPC, even though the concentration of phenolic compounds increased. This lack of significant effect was attributed to the limited interaction between enzymes and substrates when an osmotic solution permeates food tissue, hindering enzymatic activity and preventing the oxidation of phenolic compounds (Quiles et al., 2005).

# Subgroup analysis: impact of moderator variables on the quality of dried fruits

The substantial heterogeneity observed in the data obtained from the included studies led to a broad 95% CI range (Table 2). Various factors contributed to this heterogeneity, including different types of fruit, solution concentrations, types of solution, varying drying temperatures, and diverse drying methods. Consequently, a subgroup analysis was conducted based on the types of fruit, osmotic agents, solution concentrations, drying methods, and drying temperatures. The objective was to discern the influence of moderator variables on the quality of dried fruits. Of note, certain parameters, such as solution temperature, agitation, solution-to-sample ratio, and treatment duration, could not be analyzed because of limited information.

Table 2. Pooled results of the effect of osmotic pretreatment and control on the quality of dried fruits

Output variable	ns	n <sup>c</sup>	CMD	95% CI		сг		Heterogeneity (%)			
	n	n	SMD	Lower	Upper	SE	E <i>P-</i> value	Q <sub>M</sub>	DF	<i>P</i> -value	I <sup>2</sup>
ΔΕ	19	106	-4.139	-4.956	-3.321	0.417	<0.001	1,745.707	105	<0.001	93.985
TA (%)	3	16	-7.439	-10.452	-4.425	1.537	<0.001	110.255	15	<0.001	86.395
TFC (mg QE/100 g)	3	30	-1.634	-2.582	-0.686	0.484	<0.001	145.454	29	<0.001	80.062
TPC (mg GAE/100 g)	13	57	0.467	-0.290	1.224	0.386	0.227	334.674	56	<0.001	83.267
Vit B1 (mg/100 g)	3	30	-7.730	-9.737	-5.724	1.024	<0.001	230.766	29	<0.001	87.433
Vit B3 (mg/100 g)	3	30	-2.208	-3.355	-1.062	0.585	<0.001	177.255	29	<0.001	83.639
Vit C (mg/100 g)	9	41	-1.235	-3.123	0.653	0.963	0.200	347.847	40	<0.001	88.501
β-Carotene (mg/100 g)	3	22	9.275	6.204	12.347	1.567	<0.001	155.667	21	<0.001	86.510
DPPH (% RSA)	4	21	1.199	0.527	1.871	0.343	<0.001	50.117	20	<0.001	60.094

 $\Delta E$ , total color difference; TA, titratable acidity; TFC, total flavonoid content; QE, quercetin equivalent; TPC, total phenolic content; GAE, gallic acid equivalent; Vit, vitamin; DPPH, 2,2-diphenyl-1-picrylhydrazyl; RSA, radical scavenging activity; n<sup>s</sup>, number of studies; n<sup>c</sup>, number of comparisons; SMD, standardized mean difference; 95% CI, 95% confidence interval; SE, standard error; Q<sub>M</sub>, coefficient of moderators; DF, degree of freedom; I<sup>2</sup>, inconsistency index.

# Subgroup analysis: impact of types of fruit on the quality of dried fruits

In this study, a subgroup analysis was conducted to evaluate the effects of osmotic pretreatment on the qualities of dried fruits across different fruit types (Table 3). The results showed that osmotic pretreatment significantly decreased the  $\Delta E$  values (P<0.05) of dried fruits, including banana, apple, taikor, kiwi, mango, and pineapple, compared with the control. However, osmotic-dried quince and citrus exhibited a significant increase in  $\Delta E$  (P<0.05) compared with the control. Additionally, osmotic-dried citrus and pineapple showed a significant decrease in vitamin B<sub>1</sub> levels (P<0.05) compared with the control. By contrast, osmotic pretreatment did not significantly affect vitamin B<sub>1</sub> levels (P>0.05) in dried taikor. However, vitamin  $B_3$  and C levels were significantly reduced (P < 0.05) in osmotic-dried pineapple but remained unaffected (P > 0.05) in dried taikor and citrus.

Osmotic-dried pineapple showed a significant decrease (P<0.05) in TA, whereas osmotic-dried mango exhibited a minor increase (P>0.05). Furthermore, the TFC of dried pineapple decreased significantly (P<0.05) after osmotic pretreatment. On the other hand, osmotic-dried taikor and citrus did not show any significant decrease (P>0.05) in TFC compared with the control. Additionally, osmotic pretreatment significantly increased  $\beta$ -carotene levels (P<0.05) of dried taikor and pineapple. Moreover, osmotic-dried taikor and citrus showed a significant increase (P<0.05) in DPPH levels. Finally, osmotic-dried apricots exhibited a significant increase (P<0.05) in TPC compared

Table 3. Subgroup analysis: impact of types of fruit on the quality of dried fruits

Outer to reside to	Culture	CMD	95%	% CI	SE	<b>D</b> value
Output variable	Subgroup	SMD	Lower	Upper	SE	<i>P</i> -value
ΔΕ	Papaya	-1.339	-3.097	0.419	0.897	0.135
	Banana	-7.264	-12.073	-2.454	2.454	0.003
	Apple	-11.455	-13.239	-9.671	0.910	< 0.001
	Taikor	-45.051	-61.729	-28.374	8.509	<0.001
	Quince	3.043	0.278	5.807	1.411	0.031
	Kiwi	-2.585	-3.567	-1.602	0.501	<0.001
	Citrus	1.266	0.240	2.292	0.523	0.016
	Mango	-1.938	-2.555	-1.320	0.315	<0.001
	Pineapple	-1.370	-2.170	-0.570	0.408	< 0.001
Vitamin B1 (mg/100 g)	Taikor	-0.914	-2.484	0.655	0.801	0.254
	Citrus	-12,149	-16.474	-7.823	2.207	<0.001
	Pineapple	-12.807	-16.113	-9.502	1.687	<0.001
Vitamin B <sub>3</sub> (mg/100 g)	Taikor	-0.265	-1.551	1.020	0.656	0.686
	Citrus	0.413	-0.485	1.310	0.458	0.367
	Pineapple	-10.085	-12.689	-7.482	1.328	<0.001
Vitamin C (mg/100 g)	Taikor	6.772	-9.718	23.261	8.413	0.421
	Kiwi	-3.442	-7.589	0.704	2.116	0.104
	Citrus	-0.952	-2.112	0.208	0.592	0.108
	Pineapple	-98.795	-133.562	-64.029	17.738	<0.001
TA (%)	Mango	1.281	-3.406	5.969	2.392	0.592
	Pineapple	-8.924	-10.664	-7.184	0.888	<0.001
TFC (mg QE/100 g)	Taikor	-0.577	-1.405	0.252	0.423	0.172
	Citrus	-0.705	-3.969	2.559	1.665	0.672
	Pineapple	-3.026	-4.326	-1.726	0.663	<0.001
β-Carotene (mg/100 g)	Taikor	19.022	10.590	27.454	4.302	<0.001
	Pineapple	7.931	4.955	10.906	1.518	<0.001
DPPH (% RSA)	Taikor	0.794	0.084	1.504	0.362	0.028
	Citrus	0.979	0.077	1.881	0.460	0.033
TPC (mg GAE/100 g)	Papaya	2.625	-3.585	8.835	3.169	0.407
	Apricot	6.985	4.517	9.452	1.259	< 0.001
	Taikor	1.104	-0.184	2.393	0.657	0.093
	Kiwi	-2.007	-5.197	1.184	1.628	0.218
	Citrus	0.071	-1.424	1.566	0.763	0.926
	Banana	0.048	-0.877	0.972	0.472	0.920
	Apple	-0.614	-2.020	0.792	0.717	0.392
	Pineapple	0.768	-1.624	3.159	1.220	0.529

ΔE, total color difference; TA, titratable acidity; TFC, total flavonoid content; QE, quercetin equivalent; DPPH, 2,2-diphenyl-1-picrylhydrazyl; RSA, radical scavenging activity; TPC, total phenolic content; GAE, gallic acid equivalent; SMD, standardized mean difference; 95% CI, 95% confidence interval; SE, standard error. with the control.

Based on our findings, the response of different types of fruit to osmotic pretreatment varied significantly. Fruit characteristics, including species, kind, and maturity level, play a crucial role in determining the amount of mass transferred during osmotic drying (Bekele and Ramaswamy, 2010). Furthermore, the kinetics of osmotic mass transfer in food are influenced by variations in chemical content (e.g., carbohydrates, fats, proteins, and salt) and physical properties (e.g., skin, porosity, fiber orientation, and cell arrangement) (Rahman, 2007). Consequently, each fruit responded differently when subjected to osmotic pretreatment before the drying process. Drawing definitive conclusions about the ideal fruit for osmotic pretreatment was challenging because of the variations observed within each quality category. However, it could be inferred that taikor benefited most from osmotic pretreatment. This was evident through the enhanced  $\beta$ -carotene and DPPH levels, minimizing color changes and preserving vitamin B<sub>1</sub>, vitamin B<sub>3</sub>, vitamin C, TFC, and TPC.

# Subgroup analysis: impact of osmotic agents on the quality of dried fruits

In Table 4, subgroup analysis showed that different osmotic agents, including sugar, sugar alcohol, sugar-salt, fruit juice-sugar, salt, and fruit juice, had a significant effect (P<0.05) on the quality of osmotic-dried fruits. The use of sugar, sugar alcohol, and sugar-salt as osmotic agents resulted in a significant reduction (P<0.05) in the  $\Delta E$  of osmotic-dried fruits. Conversely, fruit juice-sugar led to a significant increase (P<0.05) in the  $\Delta E$  of osmotic-dried fruits compared with the control, whereas salt and fruit juice had no significant effect (P>0.05) in  $\Delta E$ .

The analysis also showed that the use of sugar and salt as osmotic agents caused a significant decrease (P < 0.05) in vitamin  $B_1$  levels in dried fruits compared with the control. Moreover, dried fruits subjected to a sugar solution experienced a significant decrease (P < 0.05) in vitamin B<sub>3</sub> levels, whereas salt treatment did not have a significant impact (P>0.05) compared with the control. Sugar had no significant effect (P>0.05) in vitamin C levels. However, salt significantly decreased (P < 0.05) vitamin C levels compared with the control. Sugar and salt had a negative effect by significantly reducing (P < 0.05) the TA and TFC of dried fruits compared with the control. However, the presence of sugar and salt significantly increased (P<0.05) the  $\beta$ -carotene and DPPH levels of osmoticdried fruits, but it did not significantly affect (P>0.05) their TPC compared with the control.

Based on the analysis results, sugar emerged as a superior osmotic agent compared with salt, showcasing its ability to maintain vitamin C and TPC, increase  $\beta$ -carotene and DPPH levels, and prevent undesirable color changes. Tortoe (2010) also suggested that high sugar

Table 4. Subgroup analysis: impact of osmotic agents on the quality of dried fruits

Outrast service bla	Culture and	CMD	95%	6 CI	<u>د</u> ۲		
Output variable	Subgroup	SMD	Lower	Upper	SE	<i>P</i> -value	
٨E	Sugar	-5.642	-6.624	-4.661	0.501	<0.001	
	SA	-2.008	-3.821	-0.194	0.925	0.030	
	Salt	-1.277	-3.980	1.427	1.379	0.355	
	FJ	3.583	-0.743	7.909	2.207	0.105	
	FJ-sugar	9.404	5.722	13.085	1.878	<0.001	
	Sugar-salt	-4.710	-6.600	-2.820	0.964	<0.001	
Vitamin B1 (mg/100 g)	Sugar	-7.338	-9.652	-5.024	1.181	<0.001	
	Salt	-9.568	-14.008	-5.127	2.266	<0.001	
Vitamin B3 (mg/100 g)	Sugar	-2.756	-4.244	-1.268	0.759	<0.001	
	Salt	-0.992	-2.758	0.774	0.901	0.271	
Vitamin C (mg/100 g)	Sugar	-0.220	-2.139	1.699	0.979	0.822	
	Salt	-12.833	-20.305	-5.361	3.812	<0.001	
TA (%)	Sugar	-7.303	-10.800	-3.807	1.784	<0.001	
	Salt	-8.112	-10.930	-5.294	1.438	<0.001	
TFC (mg QE/100 g)	Sugar	-1.275	-2.382	-0.168	0.565	0.024	
	Salt	-2.569	-4.473	-0.665	0.971	0.008	
$\beta$ -Carotene (mg/100 g)	Sugar	9.320	5.415	13.225	1.992	<0.001	
	Salt	9.257	4.578	13.937	2.388	<0.001	
DPPH (% RSA)	Sugar	1.147	0.221	2.074	0.473	0.015	
	Salt	1.481	0.732	2.230	0.382	<0.001	
TPC (mg GAE/100 g)	Sugar	0.376	-0.489	1.241	0.441	0.395	
	Salt	0.855	-0.694	2.403	0.790	0.280	

ΔE, total color difference; TA, titratable acidity; TFC, total flavonoid content; QE, quercetin equivalent; DPPH, 2,2-diphenyl-1-picrylhydrazyl; RSA, radical scavenging activity; TPC, total phenolic content; GAE, gallic acid equivalent; SA, sugar alcohol; FJ, fruit juice; SMD, standardized mean difference; 95% CI, 95% confidence interval; SE, standard error. concentrations could effectively inhibit enzymatic oxidative browning reactions, a crucial factor for preserving the quality of dried products. Interestingly, while sodium is preferred for vegetables, sugar is commonly used for fruits (Sereno et al., 2001; Yadav and Singh, 2014). The effectiveness, convenience, and desirable flavor profile of sugar have contributed to its popularity (Tortoe, 2010). Sugar alcohol and sugar-salt may hold the potential for further improving the quality of dried fruits by reducing  $\Delta E$ . However, additional research is needed to determine their impact on more qualities.

# Subgroup analysis: impact of solution concentrations on the quality of dried fruits

Table 5 presents a subgroup analysis focusing on the impact of solution concentrations on dried fruits. The results showed the significant effects (P < 0.05) of various concentrations of solutions, including sugar (1%, 30%, 40%, 45%, 61.26%, 65%, and 70%), sugar (1.8%)-salt (0.1%), sugar alcohol (30%), and fruit juice (70.3%), in  $\Delta E$  of osmotic-dried fruits. Specifically, the addition of 65.1% fruit juice significantly increased  $\Delta E$  (P<0.05). However, other solutions (2% salt; 10%, 50%, and 60% sugar; and a mixture of 70% sugar and 65.1% fruit juice) did not yield a statistically significant effect (P>0.05) in  $\Delta E$  of osmotic-dried fruits. Further analysis revealed that 1% and 10% sugar solutions significantly reduced (P <0.05) vitamin B1 and B3 levels in osmotic-dried fruits. A 2% salt solution resulted in a statistically significant reduction (P<0.05) in vitamin B<sub>1</sub> levels, but it had no significant effect (P>0.05) in vitamin B<sub>3</sub> levels. Moreover, 1% sugar and 2% salt concentrations significantly affected vitamin C loss in osmotic-dried fruits, whereas 10% and 40% sugar concentrations did not have a significant effect compared with the control. The 1% and 10% sugar and 2% salt solutions significantly decreased (P < 0.05) TA in osmotic-dried fruits compared with the control. Meanwhile, the 65% sugar solution increased the TA of osmotic-dried fruits, although not significantly (P>0.05) compared with the control. The 1% sugar and 2% salt solutions significantly decreased (P < 0.05) TFC in osmotic-dried fruits. However, the 10% sugar solution did not significantly affect (P>0.05) TFC. Unlike the 1% sugar solution, 2% salt and 10% sugar solutions significantly increased (P < 0.05)  $\beta$ -carotene levels in osmotic-dried fruits compared with the control. Meanwhile, the 2% salt solution significantly increased (P<0.05) DPPH levels in osmotic-dried fruits; however, 10% sugar solution did not have a significant effect (P>0.05) compared with the control. With regard to TPC, 10% sugar concentration significantly increased (P<0.05) the TPC of osmotic-dried fruits, whereas 40% and 45% sugar significantly reduced (P < 0.05) the TPC compared with the control. On the other hand, 1%, 60%, and 61.26% sugar and 2%

salt solutions did not have a significant effect (P>0.05) on the TPC of osmotic-dried fruits compared with the control.

Based on the available data, determining the ideal concentration for osmotic pretreatment is challenging. However, 10% sugar concentration was found to be the most effective, increasing  $\beta$ -carotene levels and TPC while preserving TFC and DPPH levels. Additionally, 2% salt solution is recommended for osmotic pretreatment as it increases  $\beta$ -carotene and DPPH levels while maintaining color, TPC, and vitamin B<sub>3</sub> levels in dried fruits. Of note, the solution concentration should not be too low as it may result in low osmotic pressure and insufficient driving force to remove water from the material (Chandra and Kumari, 2015). Conversely, high-concentration osmotic solutions have demonstrated greater efficacy in maintaining the antioxidant capacity (Landim et al., 2016).

### Subgroup analysis: impact of drying methods on the quality of dried fruits

Table 6 presents a subgroup analysis that examines the impact of various drying methods on the quality of dried fruits. Aside from vitamin C, convective drying significantly influenced (P<0.05)  $\Delta$ E, vitamin B<sub>1</sub>, vitamin B<sub>3</sub>, TA, TFC,  $\beta$ -carotene, DPPH, and TPC in osmotic-dried fruits compared with the control. Convective-explosion puffing (C-EP) drying had a significant impact (P<0.05) in  $\Delta$ E but did not significantly affect (P>0.05) TA. Instant controlled pressure drop (ICPD) drying had a significant effect (P<0.05) in  $\Delta$ E and TPC. Microwave vacuum, convective-microwave vacuum, and freeze-drying had no significant effect (P>0.05) in  $\Delta$ E. Meanwhile, infrared drying caused a significant decrease (P<0.05) in  $\Delta$ E. Lastly, vacuum drying caused a significant decrease (P<0.05) in TPC.

According to Ramya and Jain (2017), osmotic dehydration is not a reliable method for maintaining the shelf life and stability of the final product for an extended period. Therefore, other drying methods should be considered. Based on this study, convective drying was the only suitable method for analyzing all observed dried fruit qualities. Ramya and Jain (2017) suggested that this was because of the reliance on hot air drying in most artificial drying operations. When combined with osmotic pretreatment, this technique was highly effective in drying fruits as it enhanced color,  $\beta$ -carotene, DPPH, and TPC while preserving vitamin C compared with untreated samples. Known for its ability to increase water transfer, osmotic dehydration (Garcia et al., 2007) was particularly effective in shortening the drying process (Fernandes et al., 2006) and mitigating the damage caused by heating during convective drying. There is potential for combining osmotic pretreatment with infrared, ICPD, and C-EP drying methods to further enhance the color of dried fruits.

Output variable	Subgroup	SMD	95%	% CI	SE	<i>P</i> -value
Output variable	Subgroup	JMD	Lower	Upper	SE SE	
ΔΕ	1 <sup>s</sup>	-1.248	-2.427	-0.069	0.602	0.038
	1.8 <sup>s</sup> -0.1 <sup>st</sup>	-4.710	-6.600	-2.820	0.964	<0.001
	2 <sup>St</sup>	-1.277	-3.980	1.427	1.379	0.355
	10 <sup>s</sup>	-1.157	-2.768	0.454	0.822	0.159
	30 <sup>s</sup>	-1.589	-2.531	-0.647	0.481	<0.001
	30 <sup>SA</sup>	-2.008	-3.821	-0.194	0.925	0.030
	40 <sup>S</sup>	-20.543	-24.068	-17.019	1.798	<0.001
	45 <sup>s</sup>	-1.281	-2.318	-0.243	0.529	0.016
	50 <sup>s</sup>	0.243	-0.557	1.042	0.408	0.552
	60 <sup>S</sup>	-2.751	-5.732	0.230	1.521	0.070
	61.26 <sup>s</sup>	-10.268	-17.435	-3.102	3.656	0.005
	65 <sup>S</sup>	-1.938	-2.555	-1.320	0.315	<0.001
	65.1 <sup>FJ</sup>	10.764	7.517	14.012	1.657	<0.001
	70 <sup>S</sup> -65.1 <sup>FJ</sup>	6.381	-2.400	15.163	4.481	0.154
	70 <sup>s</sup>	-3.899	-5.216	-2.582	0.672	<0.001
	70.3 <sup>FJ</sup>	-21.879	-38.295	-5.463	8.376	0.009
itamin B1 (mg/100 g)	1 <sup>s</sup>	-16.069	-29.689	-2.449	6.949	0.021
	2 <sup>St</sup>	-9.568	-14.008	-5.127	2,266	<0.001
	10 <sup>s</sup>	-6.635	-8.986	-4.283	1.200	<0.001
tamin B₃ (mg/100 g)	1 <sup>s</sup>	-13.878	-25.559	-2.197	5.960	0.020
	2 <sup>St</sup>	-0.992	-2.758	0.774	0.901	0.271
	10 <sup>s</sup>	-1.991	-3.407	-0.574	0.723	0.006
/itamin C (mg/100 g)	1 <sup>s</sup>	-80.075	-111.661	-48.490	16.115	<0.001
	2 <sup>St</sup>	-12.833	-20.305	-5.361	3.812	<0.001
	10 <sup>s</sup>	0.817	-1.920	3.555	1.397	0.558
	40 <sup>s</sup>	-3.442	-7.589	0.704	2.116	0.104
A (%)	1 <sup>s</sup>	-9.843	-16.648	-3.038	3.472	0.005
	2 <sup>St</sup>	-8.112	-10.930	-5.294	1.438	<0.001
	10 <sup>s</sup>	-10.382	-12.903	-7.860	1.286	<0.001
	65 <sup>s</sup> 1 <sup>s</sup>	1.281	-3.406	5.969	2.392	0.592
FC (mg QE/100 g)	1 <sup>s</sup>	-5.347	-7.344	-3.351	1.019	<0.001
	2 <sup>St</sup>	-2.569	-4.473	-0.665	0.971	0.008
	10 <sup>s</sup>	-0.721	-1.813	0.371	0.557	0.195
-Carotene (mg/100 g)	1 <sup>s</sup>	1.988	-0.451	4.426	1.244	0.110
	oSt	0.057	4 5 7 0	10.007	2 200	10.001

Table 5. Subg

DPPH (% RSA)

TPC (mg GAE/100 g)

ΔE, total color difference; TA, titratable acidity; TFC, total flavonoid content; QE, quercetin equivalent; DPPH, 2,2-diphenyl-1-picrylhydrazyl; RSA, radical scavenging activity; TPC, total phenolic content; GAE, gallic acid equivalent; S, sugar; St, salt; SA, sugar alcohol; FJ, fruit juice; SMD, standardized mean difference; 95% CI, 95% confidence interval; SE, standard error.

4.578

10.262

0.732

-0.142

-19.522

-0.694

1.245

-2.329

-4.739

-8.266

-0.877

13.937

21.126

2.230

1.316

5.289

2.403

3.269

-0.310

-2.574

10.359

0.972

9.257

15.694

1.481

0.587

-7.116

0.855

2.257

-1.320

-3.656

1.047

0.048

#### Subgroup analysis: impact of drying temperatures on the quality of dried fruits

2<sup>St</sup>

10<sup>S</sup>

2<sup>St</sup>

10<sup>S</sup>

1<sup>s</sup>

2<sup>St</sup>

10<sup>S</sup>

40<sup>s</sup>

45<sup>S</sup>

60<sup>S</sup>

61.26<sup>s</sup>

Table 7 shows the results of subgroup analysis for drying temperatures. A drying temperature of 45°C showed statistically significant effects (P < 0.05) in the vitamin B<sub>1</sub> and  $\beta$ -carotene levels and TPC of osmotic-dried fruits. However, there was no significant effect (P>0.05) in  $\Delta E$ ,

vitamin B<sub>3</sub>, vitamin C, TFC, and DPPH compared with the control group. Similarly, a drying temperature of 50°C had a statistically significant effect (P < 0.05) in vitamin  $B_1$ , vitamin  $B_3$ , TA, TFC,  $\beta$ -carotene, and DPPH, but not in  $\Delta E$ , vitamin C, and TPC. The results further indicated that a drying temperature of 55°C significantly affected (P<0.05)  $\Delta E$ , vitamin B<sub>1</sub>, TA, and  $\beta$ -carotene, while no

2.388

2.772

0.382

0.372

6.330

0.790

0.517

0.515

0.552

4.751

0.472

< 0.001

< 0.001

< 0.001

0.114

0.261

0.280

< 0.001

0.010

< 0.001

0.826

0.920

Output veriable	Cubanaun	CMD	95%	6 CI	C.E.		
Output variable	Subgroup	SMD	Lower	Upper	SE	<i>P</i> -value	
ΔE	Convective	-5.935	-7.235	-4.635	0.663	<0.001	
	MV	-1.140	-4.407	2,128	1.667	0.494	
	C-MV	0.229	-0.433	0.891	0.338	0.498	
	Freeze	2.642	-2.816	8.100	2.785	0.343	
	Infrared	-6.027	-8.216	-3.838	1.117	<0.001	
	Microwave	0.433	-0.393	1.259	0.421	0.304	
	ICPD	-7.670	-9.348	-5.991	0.856	<0.001	
	C-EP	-1.938	-2.555	-1.320	0.315	<0.001	
′itamin B₁ (mg/100 g)	Convective	-7.730	-9.737	-5.724	1.024	<0.001	
/itamin B₃ (mg/100 g)	Convective	-2.208	-3.355	-1.062	0.585	<0.001	
/itamin C (mg/100 g)	Convective	-1.493	-3.416	0.429	0.981	0.128	
Ā (%)	C-EP	1.281	-3.406	5.969	2.392	0.592	
	Convective	-8.924	-10.664	-7.184	0.888	<0.001	
FC (mg QE/100 g)	Convective	-1.634	-2.582	-0.686	0.484	<0.001	
B-Carotene (mg/100 g)	Convective	10.220	7.219	13.221	1.531	<0.001	
)PPH (% RSA)	Convective	1.133	0.446	1.820	0.350	0.001	
PC (mg GAE/100 g)	Convective	1.254	0.397	2.110	0.437	0.004	
	Vacuum	-2.692	-4.870	-0.514	1.111	0.015	
	ICPD	-1.126	-2.048	-0.204	0.471	0.017	

Table 6. Subgroup analysis: impact of drying methods on the quality of dried fruits

ΔE, total color difference; TA, titratable acidity; TFC, total flavonoid content; QE, quercetin equivalent; DPPH, 2,2-diphenyl-1-picrylhydrazyl; RSA, radical scavenging activity; TPC, total phenolic content; GAE, gallic acid equivalent; SMD, standardized mean difference; 95% CI, 95% confidence interval; SE, standard error; MV, microwave vacuum; C-MV, convective-MV; ICPD, instant controlled pressure drop; C-EP, convective-explosion puffing.

significant effect (P>0.05) was observed for vitamin B<sub>3</sub>, vitamin C, TFC, DPPH, and TPC compared with the control. At 60°C, a significant impact (P<0.05) was observed in  $\Delta E$ , vitamin B<sub>1</sub>, vitamin B<sub>3</sub>, TA, TFC,  $\beta$ -carotene, DPPH, and TPC in osmotic-dried fruits compared with the control; however, no significant effect (P>0.05) was found in vitamin C. Compared with the control, a drying temperature of 70°C significantly affected (P<0.05)  $\Delta E$  and TPC but not vitamin C. Using a temperature combination of 90°C-95°C-70°C resulted in a significant reduction (P <0.05) in  $\Delta E$  and TPC of osmotic-dried fruits compared with the control. Furthermore, employing a temperature combination of 50°C-95°C-75°C led to a substantial decrease (P < 0.05) in  $\Delta E$  and a nonsignificant increase (P >0.05) in TA of osmotic-dried fruits compared with the control.

After conducting experiments at drying temperatures of 45°C, 50°C, 55°C, and 60°C for osmotically pretreated dried fruits, we found that a temperature of 60°C yielded the best results. This temperature not only minimized color changes but also increased the levels of vitamin B<sub>1</sub>,  $\beta$ -carotene, DPPH, and TPC while preserving vitamin C. The increase in drying temperature could shorten the drying time and enhance the effective moisture diffusivity value (Lyu et al., 2017). Additionally, employing osmotic pretreatment could further expedite the drying process (Fernandes et al., 2006). Therefore, a drying temperature of 60°C is recommended for drying fruits with osmotic pretreatment for better quality.

Based on the research findings, osmotic pretreatment yields mixed results. While it enhances certain qualities of dried fruits, such as total color difference,  $\beta$ -carotene, and DPPH, it also has negative effects in total flavonoids, vitamin B<sub>1</sub>, and vitamin B<sub>3</sub>. Generally, the bioactive compounds in fruits, including  $\beta$ -carotene, DPPH, and flavonoids, will undergo a decline when dried, but osmotic pretreatment has a differing impact on them. Compared with the control, osmotic pretreatment increases DPPH levels because it forms a barrier on the cell surface that can prevent the release of antioxidant compounds. Similarly, the formation of a barrier resulting from osmotic pretreatment can impede the entry of oxygen, thus slowing down  $\beta$ -carotene oxidation. Additionally,  $\beta$ -carotene is a constituent insoluble in water. Hence, there is no reduction in  $\beta$ -carotene because of leaching during osmotic pretreatment. Conversely, TFC is a constituent soluble in water. Thus, immersion in osmotic solution results in the loss of soluble nutrients, leading to a decrease in TFC.

The qualities of dried fruits are influenced by factors, including the type of fruit, osmotic agent, solution concentration, drying method, and drying temperature. Each fruit exhibits a different response when subjected to osmotic pretreatment. In this study, taikor benefited the most from osmotic pretreatment compared with other fruits. This is evidenced by the increase in  $\beta$ -carotene and DPPH levels; reduction in color changes; and preservation of vitamin B<sub>1</sub>, vitamin B<sub>3</sub>, vitamin C, TFC, and TPC compared with the control. To enhance the quality of

Output veriable	Cubanaun	SMD	955	% CI	C.E.	<i>P</i> -value
Output variable	Subgroup		Lower	Upper	SE	
ΔE	45	-3.941	-8.700	0.818	2.428	0.105
	50	-1.295	-3.048	0.459	0.895	0.148
	55	-30.757	-36.312	-25.202	2.834	<0.001
	60	-1.008	-2.001	-0.016	0.507	0.047
	70	-1.371	-2.367	-0.375	0.508	0.007
	-40	2.642	-2.816	8.100	2.785	0.343
	90-95-70	-7.670	-9.348	-5.991	0.856	<0.001
	50-95-75	-1.938	-2.555	-1.320	0.315	<0.001
Vitamin B1 (mg/100 g)	45	-5.895	-9.157	-2.633	1.664	<0.001
	50	-7.317	-10.949	-3.686	1.853	<0.001
	55	-7.256	-10.927	-3.586	1.873	<0.001
	60	-17.070	-23.863	-10.278	3.466	<0.001
Vitamin B₃ (mg/100 g)	45	-0.018	-1.488	1.453	0.750	0.981
J (	50	-2.661	-4.738	-0.584	1.060	0.012
	55	-1.776	-3.770	0.217	1.017	0.081
	60	-11.797	-16.785	6.810	2.545	< 0.001
Vitamin C (mg/100 g)	45	-1.274	-4.941	2.392	1.871	0.496
vitaliliti e (ilig/100 g)	50	-2.123	-6.535	2.289	2.251	0.346
	55	-0.300	-6.076	5.476	2.947	0.919
	60	-1.354	-6.564	3.857	2.658	0.611
	70	-2.518	-5.461	0.424	1.501	0.093
TA (%)	50	-11.303	-14.306	-8.301	1.532	< 0.001
()())	55	-10.088	-13.084	-7.091	1.529	< 0.001
	60	-6.718	-8.875	-4.560	1.101	<0.001
	50-95-75	1.281	-3.406	5.969	2.392	0.592
TFC (mg QE/100 g)	45	-0.782	-2.764	1.199	1.011	0.439
	50	-2.482	-3.748	-1.216	0.646	<0.001
	55	-0.286	-2.375	1.804	1.066	0.789
	60	-3.388	-4.655	-2.121	0.646	< 0.001
3-Carotene (mg/100 g)	45	6.946	3.790	10.102	1.610	< 0.001
s carotone (mg, roo g,	50	14.550	5.852	23.247	4.437	0.001
	55	9.577	4.033	15.121	2.829	< 0.001
	60	15.229	4.839	25.618	5.301	0.004
DPPH (% RSA)	45	0.544	-0.141	1.229	0.349	0.120
	50	0.881	0.172	1.590	0.362	0.015
	55	1.414	-0.201	3.029	0.824	0.086
	60	7.269	1.173	13.364	3.110	0.019
FPC (mg GAE/100 g)	45	1.384	0.654	2.115	0.373	<0.001
	50	1.136	-0.964	3.236	1.071	0.289
	55	0.623	-1.116	2.361	0.887	0.483
	60	2.736	0.289	5.184	1.249	0.028
	70	-2.536	-4.182	-0.890	0.840	0.023
	90-95-70	-1.126	-2.048	-0.204	0.471	0.003

Table 7. Subgroup analysis: impact of drying temperatures on the quality of dried fruits

ΔE, total color difference; TA, titratable acidity; TFC, total flavonoid content; QE, quercetin equivalent; DPPH, 2,2-diphenyl-1-picrylhydrazyl; RSA, radical scavenging activity; TPC, total phenolic content; GAE, gallic acid equivalent; SMD, standardized mean difference; 95% CI, 95% confidence interval; SE, standard error.

dried fruits, a 10% sugar solution is an effective additive. Moreover, osmotic dehydration should be combined with convective drying at a temperature of 60°C for optimal results in the drying process. The findings of this study can provide valuable insights and future research paths to improve the quality of dried fruits.

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### AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

### AUTHOR CONTRIBUTIONS

Concept and design: TY, WA. Analysis and interpretation: TY, WA. Data collection: TY, WA, MNA, LKH, TEPM, HDH, A, PYF, DA, MMJL. Writing the article: TY, WA. Critical revision of the article: AJ. Final approval of the article: all authors. Statistical analysis: TY, WA. Obtained funding: WA. Overall responsibility: all authors.

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