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Application of the Simplex Lattice Design Methode to Determine the Optimal Formula Nanoemulsion with Virgin Coconut Oil and Palm Oil

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Abstract
Background*: The success of nanoemulsion preparation is characterized by characteristics such as small droplet size, polydispersity index (PDI), and % transmittance, which are close to 100%. One of these factors is the type of oil component used. The Simplex Lattice Design (SLD) method can be used to determine the ratio of oil combinations to obtain an optimal nanoemulsion formula.* ***Objective****: The application of the Simplex Lattice Design (SLD) method can help researchers speed up the acquisition of optimal formulas without trial and error so that nanoemulsion formulas that meet specifications can be obtained.* ***Methods****: This research uses the Simplex Lattice Design (SLD) method with Design of Expert Version 13 software, with an upper limit value for oil (VCO and Palm Oil) of 2.66% and a lower limit value for oil (VCO and Palm Oil) of 0, which then The results of several formulas come out and characterization testing is carried out to get the best formula from the recommendations produced by the software.* ***Results****: The results of the Simplex Lattice Design (SLD) showed that oil affected the droplet size and PDI (p <0.05). Six optimal formulas were obtained, and after testing in the laboratory, there was no significant difference between the results of the SLD program and those of the laboratory (Sig. <0.05).* ***Conclusion****: This study shows that the Simplex Lattice Design (SLD) method is very effective.*

Keywords*: design expert, nanoemulsion, simplex lattice design (SLD)*

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INTRODUCTION

A nanoemulsion is a dispersion system of oil-in-water or water-in-oil with an average droplet size of 10-100 nanometers. Nanoemulsions are composed of several components, including oil, water, and surfactants (Ghasamiyeh & Samani, 2020). Nanoemulsions have the advantage of low toxicity, are non-irritating, increase the solubility of active ingredients, increase bioavailability, have long-term stability, and are very suitable for application in preparations by the dermal and transdermal routes (Jadhav et al., 2020).

The formation of nanoemulsions is influenced by three factors: oil selection, surfactant selection, and co-surfactant type selection. In this study, the researchers focused on the oil selection factor. In general, there are three types of oils that can be used as the oil phase in nanoemulsions: animal oils, vegetable oils, and single fatty acids such as oleic acid. Vegetable oils are considered safer than animal oils; in terms of hypersensitivity, vegetable oils are more acceptable than animal oils because animal oils often cause unacceptable odors. The vegetable oils used in this study were virgin coconut and palm oils. Both oils have different components that produce different effects in terms of the characteristics of the produced nanoemulsion. Virgin coconut oil has a lauric acid component (C12), which is a Medium Chain Triglyceride (MCT), so it produces a smaller nanoemulsion droplet size compared to oils containing long-chain triglycerides (LCT), such as palm oil, which has an oleic acid component (C18) (Erawati et al., Droplet size will affect transmittance or clarity; the smaller the droplet size, the clearer the nanoemulsion formed (Huda & Wahyuningsih, 2016). The combination of Virgin Coconut Oil (VCO) and palm oil was achieved because palm oil has a higher melting point than Virgin Coconut Oil (VCO), which increases the physical stability of the nanoemulsion. In addition, the difference in the refractive index between Virgin Coconut Oil (VCO) and palm oil can control the clarity or transmittance of the nanoemulsion.

The development of pharmaceutical preparations requires expertise in optimizing preparations such that preparations that match the desired specifications are obtained. In the world of dosage formulations, there are several optimization methods, one of which is the Simplex Lattice Design (SLD) method. The SLD method was used to determine the optimal formula for the mixture of ingredients (Teurupun et al., 2020). The Simplex Lattice Design (SLD) method is an experimental design that can be used to obtain the optimal oil combination ratio for nanoemulsions more quickly and effectively to avoid trial and error optimization (Dwiputri et al., 2022). The Simplex Lattice Design (SLD) method has been successfully used to design optimal formulas in several studies, including asiaticoside nanoemulsion (Li et al., 2020), furosemide SNEEDS (Nandita et al., 2021), ginger extract nanoemulsion (Ningsih et al., 2020), and quercetin self-nanoemulsion (Pratiwi et al., 2018).

MATERIALS AND METHODS

The ingredients used were virgin coconut oil (VCO) (cosmetic grade), palm oil (cosmetic grade), Span 80 (Industria Chimica Panzeri S.r.I) (pharmaceutical grade), Tween 80 (Industria Chimica Panzeri S.r.I) (pharmaceutical grade), absolute ethanol (Chemindo) (pharmaceutical grade), and distilled water.

Tools

Magnetic stirrer, Beakerglass, Analytical scale, ultrasonic cleanser, particle size analyzer (Delsa^{TM} Nano C, Us), and UV-Vis Spectrophotometer.

Method

Optimization of Nanoemulsion Formulas with SLD

The optimal combination ratio for nanoemulsion formulation was determined using Design-Expert software version 13 using the Simplex Lattice Design (SLD) method. The oil combination ratio obtained was 14. The two-component factor that becomes the independent variable are Virgin Coconut Oil (VCO) and palm oil, with a total oil of 2.66%, which refers to the results of research conducted by Erawati et al. (2017) but in the research undertaken by Erawati et al. (2017) only used a single oil, namely VCO. The dependent variables or responses produced were droplet size, polydispersity index (PDI), and % transmittance.

Table 1. Formula of nanoemulsion

Ingredients	Concentration (%)
Virgin Coconut Oil (VCO) Palm Oil	Total 2,6%
Span 80	1,92
Tween 80	18,66
Absolute ethanol	3,42
Buffer Solution pH 5,0±0,2	Ad 100

The process of making The combination of VCO and palm oil nanoemulsion was prepared by mixing and stirring at 44°C and 500 rpm for 3 min, followed by the addition of surfactant and stirring at 44°C and 850 rpm for 5 min. The co-surfactant was then added and stirred at the same temperature, speed, and time. Aqua dest was then added dropwise until it ran out and stirred at 1200

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rpm for 5 min. Subsequently, the nanoemulsion was sonicated at temperatures below 40 °C for 3 × 10 min.

Characterization of Nanoemulsions

Droplet size and PDI

This test used a particle size analyzer (Delsa™ Nano C, US). The nanoemulsion was inserted into a cuvette and placed in the tool. The droplet size and PDI values were obtained.

%Transmittance

This test used a UV-Vis spectrophotometer with a wavelength of 650 nm. The nanoemulsion is inserted into the cuvette and placed into the tool. The resulting data were obtained as %transmittance values.

RESULTS AND DISCUSSION

Formula Optimization

Optimization of the oil combination ratio began with 14 initial combination ratios obtained from Design-Expert software version 13. In this SLD method optimization, there are two independent variables, virgin coconut oil and palm oil, with dependent variables, namely droplet size, PDI, and % transmittance. The components of the oil combination ratio (upper limit value of 2.66 and lower limit value of 0) obtained are listed in Table 2. After obtaining 14 oil combination ratios, nanoemulsions were prepared; the data on the results of the dependent variable (nanoemulsion characteristics) are presented in Table 2. The physical appearance of the nanoemulsions is shown in Figure 2.

From the results in Table 2, the ANOVA test is continued to obtain the appropriate mathematical model of each of the dependent variables so that the effect of the oil combination on each variable is known. The criterion for acceptance of a mathematical model is that for a mathematical model, the significance of the model must be significant, and the importance of the lack of fit must not be significant (Bolton, 1997). The results of the mathematical model are listed in Table 3.

Table 2. Components oil combination ratio and results of nanoemulsion characterization

Formula	VCO (%)	Palm Oil (%)	Y1	Y2	Y3
1	0.000	2.660	14.7	0.299	87.2
2	0.736	1.923	19.5	0.298	86.6
3	1.312	1.347	19.8	0.294	96.4
4	2.256	0.040	18.5	0.133	88.0
5	1.024	1.638	16.8	0.126	91.9
6	0.000	2.660	13.2	0.398	87.2
7	1.895	0.764	15.6	0.224	87.5
8	2.660	0.000	19.6	0.200	96.3
9	0.736	1.923	19.8	0.399	80.1
10	1.600	1.059	16.3	0.147	93.1
11	1.895	0.764	16.9	0.139	97.0
12	0.736	1.923	25.6	0.297	86.5
13	0.346	2.313	16.6	0.227	97.6
14	2.660	0.000	19.9	0.130	96.9

Information : Y1 : Droplet siz; Y2 : PDI; Y3 : %Transmittance

Table 3. Results of the SLD Mathematical Model

Response	Model	*p*-value	Lack of fit
Y1	Cubic	0.0289 (significant)	0.5124 (not significant)
Y2	Linear	0.0052 (significant)	0.2805 (not significant)
Y3	Linear	0.1054(not significant)	0.1899 (not significant)

Information : Y1 : Droplet siz; Y2 : PDI; Y3 : %Transmittance

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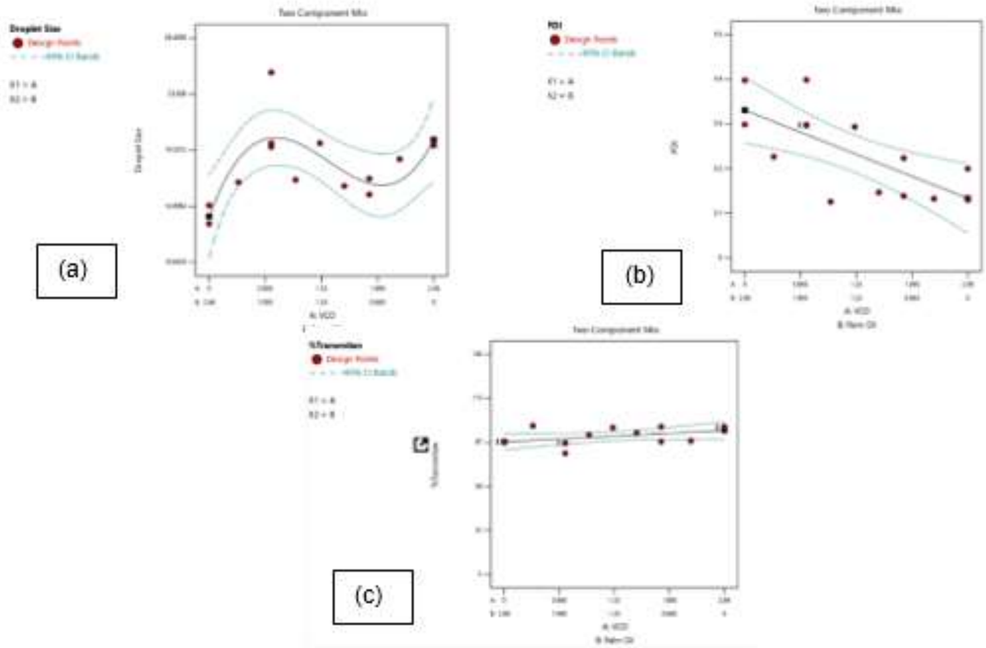

Figure 1. The normal plot of the residual of responses: (a) droplet size; (b) PDI; (c) %transmittance

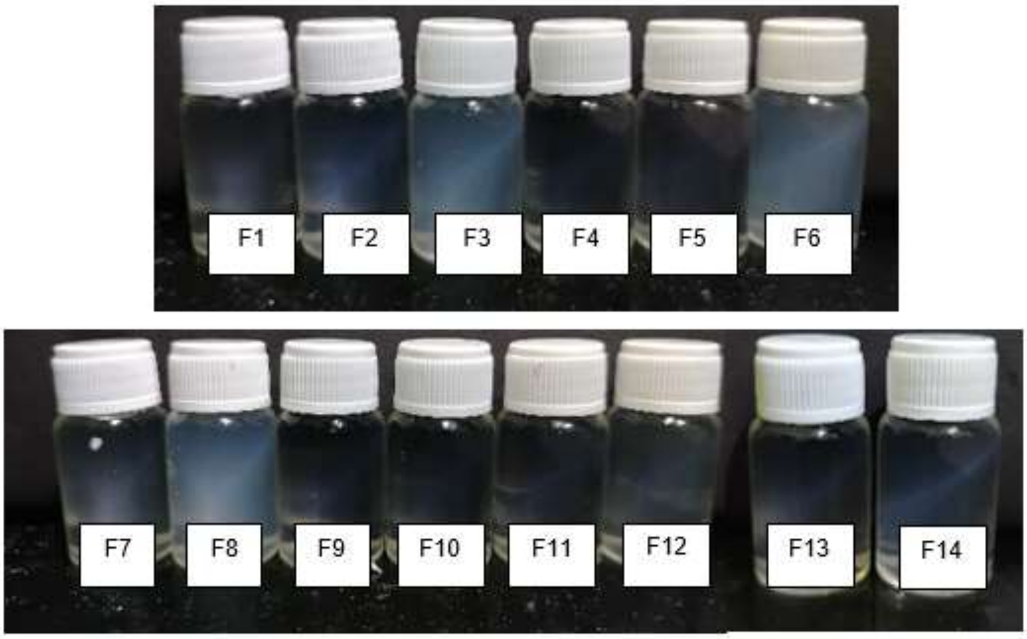

Figure 2. Appearance of 14 nanoemulsion formula SLD results

The results in Table 3 and Figure 1 show that there is an influence of the combination of oils on the droplet size (Y1) and PDI (Y2), as evidenced by the p-value (<0.05) and lack of fit (>0.05). Meanwhile, in the %transmittance response (Y3), there was no influence between the oil combinations on %transmittance, as evidenced by the p-value (>0.05). This is in accordance with the literature, which explains that differences in oil components affect the droplet size and PDI. The two oils have different components that produce different effects in terms of the characteristics of the produced nanoemulsion. Virgin coconut oil has a lauric acid component with a medium carbon atom chain (C12), which causes the nanoemulsion droplet size to be smaller than oils containing long carbon atom chains, such as palm oil containing oleic acid (C18) (Rachman et al., 2023). The PDI value is related to the stability of the nanoemulsion; the more uniform the droplet size produced, namely with a PDI value <0.5, the more stable the system will be for a long time because it can

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minimize the occurrence of flocculation in the nanoemulsion (Bashir et al., 2021). The % transmittance value was considered insignificant or had no effect. This is because the droplet sizes produced in this optimization are all small, so the nanoemulsion produced has a clarity or % transmittance with almost the same value. However, in terms of physical appearance, there are differences in the clarity of each nanoemulsion produced, in accordance with the research conducted by Apriliya et al. (2021), which explains that the% transmittance is influenced by droplet size; the smaller the droplet size, the higher the % transmittance.

Comparison of optimization results of SLD and laboratory programs

According to the formula optimization using the Simplex Lattice Design (SLD) method, six formula predictions were obtained. To determine the optimal formula, it must have a desirability value close to 1 (Bolton, 1997). In this study, all formulas had a desirability value of 1. The results of the formula predictions based on the SLD program are listed in Table 4.

The prediction results of the formula based on the SLD program were verified in the laboratory. This proves that the Simplex Lattice Design method is effective in being used as a background for formula optimization. To determine whether there is a difference between the results of the SLD Program and the laboratory, statistical testing was performed using the paired t-test method. If there was a difference, the significance value was <0.05; however, if there was no difference, the significance value was >0.05. The results of the formula predictions based on the laboratory data are presented in Tables 5, 6, and 7.

According to Table 5. The droplet size prediction formula between the prediction value and the verification value has no significant differences (>0.05), indicating that the SLD method on the droplet size variable can be considered effective in determining the optimal formula because it produces results that are not different.

According to Table 6. The PDI prediction formula between the prediction value and the verification value has no significant differences (>0.05), indicating that the SLD method on the PDI variable can be considered effective in determining the optimal formula because it produces results that are not different.

Table 5. Comparison of droplet size prediction formula results based on SLD programs and laboratories

Formula	Predicted Values	Verified Values	Sig. Value
FP1	16.5	17.6	0.414
FP2	18.3	17.4	
FP3	17.1	16.9	
FP4	16.4	14.9	
FP5	16.4	16.8	
FP6	19.6	18.6	

Table 6. Comparison of PDI prediction formula based on SLD programs and laboratories

Formula	Predicted Values	Verified Values	Sig. Value
FP1	0.190	0.192	0.946
FP2	0.227	0.263	
FP3	0.207	0.127	
FP4	0.173	0.280	
FP5	0.186	0.236	
FP6	0.250	0.149	

Table 7. Comparison of %transmitan prediction formula based on SLD program and laboratories

Formula	Predicted Values	Verified Values	Sig. Value
FP1	92.5	88.9	0.190
FP2	91.2	96.5	
FP3	91.9	95.8	
FP4	93.1	93.7	
FP5	92.7	99.6	
FP6	90.3	91.3	

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Based on Table 7. The %transmittance result of the formula prediction between the prediction value and the verification value is not significant (>0.05), meaning that the SLD method on the %transmittance variable can be said to be effective in determining the optimal formula because it produces a result that is not different. This is also in line with the research conducted by Mahiya et al. (2022), which explains that there is no significant difference between the results of the SLD program and laboratory observations, so it can be said that the SLD method is effectively used in the formula optimization. Research conducted by Amrina et al. (2024) also explains that the results of the SLD program and the actual formula of patikan kebo extract cream are not significantly different; therefore, the SLD program is considered effective for determining the optimal formula. The predicted Formula (FP) 5 is the most optimal because it has a desirability value of 1 with the best characteristics. The optimal nanoemulsion is a nanoemulsion with a small droplet size (10–100 nm), small PDI (<0.5), and % transmittance close to 100% (Das et al., 2020; Huda & Wahyuningsih, 2016). The smaller the droplet size, the more stable the nanoemulsion is (Son et al., 2019). The smaller the droplet size, the higher the %transmittance of the nanoemulsion. Nanoemulsions with high %transmittance make the preparation more acceptable, especially for cosmetics (Rakhma et al., 2021). The smaller the PDI value, the more uniform or homogenous the nanoemulsion droplets are, thus making the nanoemulsion stable for a long time (Gao & Li, 2023).

CONCLUSION

This research shows that the Simplex Lattice Design (SLD) method is very effective. This can be observed in the optimal formula obtained from the formula prediction results. It can also be seen from the comparison between the prediction result of the formula-based program SLD and the result verification that there is no significant difference, so the optimal formula can be continued for nanoemulsion development. The predicted Formula (FP) 5 is the most optimal because it has a desirability value of one with the best characteristics.

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AUTHOR CONTRIBUTIONS

Conceptualization: P.F., T.E., and N.R..; Methodology: P.F., T.E., N.R. Software: P. F. Validation: P.F., T.E., and N.R. Formal analysis, P. F. Investigation: P. F. Resources: P.F., T.E.and, N.R. Datata Curation: P.F., T.E., and N. R. Writing Original Draft: P. F. Writing - Review and Editing; P.F., T.E., and N.R. Visualization: P.F., T.E., and N.R. Supervision: P.F., T.E., and N.R. Project Administration: P.F., T.E., N.R. Funding Acquisition: P.F., T.E., and N.R.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

Amrina, F., Purwanto, A., & Riauwati, R. (2024). Optimasi Formula Krim Ekstrak Etanol Daun Patikan Kebo (Euphorbia Hirta L.) Dengan Metode Simplex Lattice Design. *Jurnal Insan Farmasi Indonesia*, *7*(2), 53-65.

Aprilya, A., Rahmadevi, R., & Meirista, I. (2021). Formulasi Nanoemulsi dengan Bahan Dasar Minyak Ikan (Oleum Iecoris Aselli): Nanoemulsion Formulation with Fish Oil (Oleum Iecoris Aselli) Base Ingredients. *Jurnal Sains Dan Kesehatan*, *3*(3), 370-375.

Bashir, M., Ahmad, J., Asif, M., Khan, S. U. D., Irfan, M., Y Ibrahim, A., ... & AS Abourehab, M. (2021). Nanoemulgel, an innovative carrier for diflunisal topical delivery with profound anti-inflammatory effect: In vitro and in vivo evaluation. *International Journal of Nanomedicine*, 1457-1472.

Bolton, S.. 1997. *Pharmaceutical Statistics : Practical and Clinical Applications, 3 rd Ed*, Marcel Dekker Inc., New York.

Das, S. S., Verma, P. R. P., & Singh, S. K. (2020). Screening and preparation of quercetin doped nanoemulsion: Characterizations, antioxidant and anti-bacterial activities. *LWT*, *124*, 109141.

Dwiputri, A. S., Pratiwi, L., & Nurbaeti, S. N. (2022). Optimasi Formula Sabun Organik Sebagai Scrub Kombinasi VCO, Palm Oil, Dan Olive Oil Menggunakan Metode Simplex Lattice Design. *Jurnal Mahasiswa Farmasi Fakultas Kedokteran UNTAN*, *6*(1).

Erawati, T., Firdaus, A. W., & Soeratri, W. (2017). Virgin coconut oil as oil phase in tretinoin nanoemulsion. International Journal of Drug Delivery Technology, 7(1).

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Gao, L., & Li, B. (2023). The Effects of Surfactant and Metal Ions on the Stability and Rheological Properties of Nanoemulsions Loaded with Gardenia Yellow Pigment. *Applied Nano*, *4*(2), 61-74.

Ghasemiyeh, P., & Mohammadi-Samani, S. (2020). Potential of nanoparticles as permeation enhancers and targeted delivery options for skin: Advantages and disadvantages. Drug design, development and therapy, 3271-3289.

Huda, N., & Wahyuningsih, I. (2016). Karakterisasi self-nanoemulsifying drug delivery system (SNEDDS) minyak buah merah (Pandanus conoideus Lam.). *Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia*, *3*(2), 49-57.

Jadhav, R. P., Koli, V. W., Kamble, A. B., & Bhutkar, M. A. (2020). A review on nanoemulsion. *Asian Journal of Research in Pharmaceutical Science*, *10*(2), 103-108.

Li, H., Peng, Q., Guo, Y., Wang, X., & Zhang, L. (2020). Preparation and in vitro and in vivo study of asiaticoside-loaded nanoemulsions and nanoemulsions-based gels for transdermal delivery. *International Journal of Nanomedicine*, 3123-3136.

Mahiya, M., Ratnasari, D., & Utami, M. R. (2022). Optimasi Formula SNEDDS (Self-Nanoemulsifying Drug Delivery System) Ekstrak Daun Kejibeling Menggunakan Metode SLD (Simplex Lattice Design). *Jurnal Ilmiah Wahana Pendidikan*, *8*(11), 124-129.

Nandita, S. P., Kuncahyo, I., & Harjanti, R. (2021). Formulation and Optimization of Furosemide Snedds With Variation Concentration of Tween 80 and PEG. *Journal of Fundamental and Applied Pharmaceutical Science*, *2*(1).

Ningsih, I. Y., Faradisa, H., Cahyani, M. D., Rosyidi, V. A., & Hidayat, M. A. (2020). The formulation of ginger oil nanoemulsions of three varieties of ginger (Zingiber officinale Rosc.) as natural antioxidant. *J. Res. Pharm.(Online)*, *24*, 914-924.

Pratiwi, G., Ramadhiani, A. R., Shiyan, S., & Chabib, L. (2024). Combination Simplex Lattice Design Modelling with Chemometrics Analysis for Optimization Formula Self-Nano Emulsion Loaded Quercetin.

Rachman, E. S., Soeratri, W., & Erawati, T. (2023). Characteristics and Physical Stability of Nanoemulsion as a Vehicle for Anti-Aging Cosmetics: A Systematic Review. *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia Vol*, *10*(1), 62-85.

Rakhma, D. N., Nailufa, Y., Najih, Y. A., & Wahjudi, H. (2021). Optimization Of Skin Moisturizer Formula Based On Fixed Oil (VCO, Olive Oil, And Jojoba Oil): Optimasi Formula Pelembab Kulit Berbasis Minyak Nabati (VCO, Minyak Zaitun dan Minyak Jojoba). *Journal Pharmasci*, *6*(2), 109-114.

Son, H. Y., Lee, M. S., Chang, E., Kim, S. Y., Kang, B., Ko, H., ... & Kim, Y. (2019). Formulation and characterization of quercetin-loaded oil in water nanoemulsion and evaluation of hypocholesterolemic activity in rats. *Nutrients*, *11*(2), 244.

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